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THE NATIONAL HALOTHANE STUDY

A STUDY OF THE POSSIBLE ASSOCIATION BETWEEN HALOTHANE ANESTHESIA AND POSTOPERATIVE HEPATIC NECROSIS

Report of
The Subcommittee on the National Halothane Study,
of the Committee on Anesthesia, Division of Medical Sciences,
National Academy of Sciences-National Research Council
Washington, D.C.

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FOREWORD

The National Halothane Study is a statistical and pathologic investigation of the possible association between halothane anesthesia and postoperative hepatic necrosis, and an examination of the effect of general anesthetic agents, including halothane, on postoperative mortality. The data collected constitute, in addition, a great body of information on hepatic pathology and on over-all mortality in surgical patients. The design of the Study may serve as a useful guide for the clinical pharmacologist or other investigator who wishes to study rare untoward events in medicine. And the statistical techniques devised especially for the Study are immediately and widely applicable to projects, both experimental and observational, in which allowance must be made for multiple interacting variables.

The text of this report ranges from general clinical discussion to highly technical statistical detail. The presentation is organized to allow the reader easy access to those parts in which he may have special interest. For those who wish to go directly to a summary of findings, separate, relatively detailed summaries and conclusions are presented for the study of hepatic necrosis (Chapter III - 5) and for the study of death rates (Chapter IV - 8). The Subcommittee's recommendations, which it is hoped will be of special interest to the medical profession, are presented at the conclusion of the report (Part VI).

A task of this magnitude could not have been accomplished without the extraordinary dedication of the very large group of participants. For some the Study represented a response to the need to solve an urgent problem in the practice of anesthesia; for others it was necessary to define the importance of the problem as a public health issue. For many the Study offered opportunities for new and experimental approaches to the collection, analysis, and interpretation of epidemiologic data. And for all it was an irresistible challenge.

Our special thanks are extended to R. Keith Cannan, Chairman of the Division of Medical Sciences, National Academy of Sciences-National Research Council, for his continued support and encouragement; to E. M. Papper, Chairman of the Committee on Anesthesia of the Division of Medical Sciences, and Carl R. Brewer, Project Officer of the National Institute of General Medical Sciences for the National Halothane Study, who recognized the need for the Study and were largely responsible for its activation; to Sam F. Seeley, for the wisdom and efficiency with which he provided administrative assistance; and to William H. Forrest, Jr., who, with ingenuity, skill, and perseverance, coordinated collection and analysis of the vast amount of data necessary for successful completion of the Study.

Preparation and distribution of approximately 3000 tissue slides to members of the Pathology Panel were supervised by Major General Joe M. Blumberg, Director, Armed Forces Institute of Pathology; Paul R. Glunz and Kamal G. Ishak, of the Hepatic Branch; and Lee Luna and Walter McAllister, of the Histopathology Laboratory.

Procurement and processing of basic data were coordinated by the staff of the Sutter Research Foundation: Dana J. Bach, Edna J. Collins, Beth Ann Hapgood, Velma J. Holmes, and Mary J. Wallace.

The great task of data management, including coding, editing, and error checking, was supervised by William H. Forrest, Jr., working in close collaboration with the principal investigators at the several institutions. To make the data available in a form suitable for high-speed computation, John P. Gilbert supervised the preparation and introduction of the data onto magnetic tape and wrote programs for the initial analyses. Dr. Forrest also managed the data for the study of hepatic necrosis, and he and Dr. Gilbert aided with the statistical analysis.

The main program of computing was carried out at the Stanford Computation Center, and additional computing was done at the Harvard Computing Center. In those institutions, Lawrence G. Tesler, Kerstin Bengtsson, Alberta Bryan, Michael L. Goodman, and William S. Mosteller assisted in the preparation of computer programs. Cleo Youtz assisted in mathematical analysis and in editing the final manuscript of Part IV.

The manuscript was prepared largely at Stanford and at Harvard, with the assistance of the following staffs: Stanford Department of Anesthesia: Adena Goodart, Lee Amideo, and Jacqueline Hardy; Stanford Department of Statistics: Ginnie Currey and Margaret Cline; Harvard Department of Statistics: Monica Anvoner, Linda Falcone, Lynn Holtz, Nancy Larson, Holly Lasewicz, Louise Rothman, and Patricia Scott; Harvard Department of Anesthesia: Helen T. Gallahue; and Bell Telephone Laboratories: Elizabeth L. La Jeunesse.

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Among our statistical colleagues, Raj Bahadur, James R. Boen, K. A. Brownlee, W. G. Cochran, Arthur P. Dempster, Leo A. Goodman, William Kruskal, Paul Meier, Rupert G. Miller, Jr., Charles Stein, and David L. Wallace have been generous with their advice.

John P. Bunker
Chairman
Subcommittee on the National
Halothane Study

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PART I. HISTORICAL BASIS OF THE STUDY

CHAPTER I-1. INTRODUCTION

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BACKGROUND OF THE STUDY

After extensive laboratory investigation, halothane (Fluothane), 2-bromo-2-chloro-1,1,1-trifluoroethane, was introduced to clinical anesthesia in England in 1956 and in the United States in 1958. Careful consideration had been given to the possibility that halothane, in common with many other halogenated compounds, might damage the liver, but in its early years of use it appeared to have an impressive record of safety. Studies of hepatic function in the experimental animal and in man gave no indication of halothane-induced hepatic damage. However, isolated reports of massive hepatic necrosis after halothane anesthesia soon appeared and suggested the need for further investigation. In December 1961, the Committee on Anesthesia of the National Academy of Sciences-National Research Council 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 percent, but the number of deaths attributable to massive hepatic necrosis was thought to be very small, perhaps one in 10,000 operations. No data were available on the incidence of hepatic necrosis in patients receiving other anesthetic agents or on the role of pre-existing hepatic disease, viral hepatitis, or prolonged operative shock as etiologic factors in postoperative hepatic failure. For these reasons, preliminary plans for a randomized clinical trial were drawn up 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 1963 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 enough potential value to justify the most careful examination of its imputed risk, as well as its over-all safety.

Before the Subcommittee completed its plans for a cooperative study, several additional cases of hepatic necrosis were reported. Some institutions had begun to restrict 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 might 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 with the exacting requirements of the proposed 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 4-year period 1959 through 1962; 34 met the requirements of the protocol and their data constitute the basis of this report.

OBJECTIVES OF THE STUDY

The primary objective of the Study was to compare halothane with other general anesthetics regarding incidence of fatal massive hepatic necrosis within 6 weeks of anesthesia. An equally important objective was a comparison regarding total hospital mortality within 6 weeks of anesthesia, because it was recognized that, even if halothane were responsible for death from

hepatic necrosis more often than other anesthetics, the incidence would probably be small compared with an estimated over-all operative mortality of approximately 2 percent. Indeed, a slight superiority in over-all mortality for halothane could well outweigh any excess of deaths resulting from massive hepatic necrosis.

GENERAL SCOPE OF THE STUDY

It was anticipated that the incidence of fatal massive hepatic necrosis could be very small, and that differences among anesthetics in their effect on total mortality might also be small. If death rates are about 2 percent and it is desired to detect differences measured in tenths of 1 percent, then it is necessary to take a sample large enough to include many thousands of deaths. The experience of one 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 4-year period was chosen, and the participation of many hospitals served to broaden the medical experience on which any conclusions ultimately would be based. Because it was in 1963 that several new reports of massive hepatic necrosis after halothane anesthesia precipitated widespread concern, and because that concern may well have influenced the selection of anesthetics from then on, the survey was limited to the 4-year period 1959 through 1962.

The protocol was designed to generate the data summarized briefly below and presented in detail in Part II.

Deaths

To determine the number of deaths, the protocol required each hospital to report postoperative deaths that occurred in the hospital within 6 weeks of general anesthesia, and to abstract the case records, categorizing them by the anesthetic agents used at the patients' last operations.

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 anesthesia 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 on deaths and population sample was used to calculate crude death rates for the different anesthetic agents and to adjust them for differences in type of operation and such other variables as age, sex, and preoperative physical status.

Massive Hepatic Necrosis

Each death that was thought to represent massive hepatic necrosis was reported and a photocopy of the patient's chart and 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 section submitted and estimate the degree of necrosis without knowledge of the anesthetic agent or the clinical history; and then (2) review an abstract of the clinical history, again with the anesthetic agent unknown, and express an opinion as to the possible etiology of 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 of general anesthesia of all types;

(2) for the random sample of general anesthetics, a list of individual cases giving the chart number and date of operation for each;

(3) a list of all hospital deaths occurring within 6 weeks of the administration of a general anesthetic, including the patients' chart numbers and dates of deaths;

(4) coded abstracts of the clinical records of all patients who died within 6 weeks of general anesthesia and of those identified in the random sample, including 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, anesthetic agents used, physical status (evaluated preoperatively), duration of anesthesia, operations in the previous 4 years (100 two-digit operation codes were provided for coding operative procedures), and previous exposure to halothane;

(5) a list of final diagnoses for each abstracted death that was necropsied; and

(6) photostatic copies of the relevant portions of the clinical record and blocks or slides of hepatic tissue from each case with indications of massive hepatic necrosis, possible massive hepatic necrosis, or hepatitis.

CHAPTER I-2. PHARMACOLOGY OF HALOTHANE

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This chapter offers a brief summary of the pertinent pharmacologic features of halothane. In certain areas our knowledge is not definitive or complete in spite of a large volume of reports. Moreover, clinical attributes of halothane are not always clearly defined, in that they can be influenced by the manner in which it is administered and by the physical status of the patient.

More detailed information is available in several reviews and monographs, for example, those by Johnstone (29), Stephen and Little (65), Sadove and Wallace (55), Papper and Kitz (47), Ngai (42), Price and Cohen (48), and Severinghaus and Larson (63).

PHYSICAL AND CHEMICAL PROPERTIES

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane; Fluothane) is a heavy, colorless, and volatile liquid with a molecular weight of 197, a boiling point of 50.2 C, and a vapor pressure at 20 C of 243 mm Hg. Thymol (0.01 wt percent) is added to the liquid as a stabilizer. When stored in tinted glass containers or in clinical vaporizers and protected from light, halothane is stable and degradation products are not found even after long periods. Before 1965, commercial halothane contained certain impurities in trace amounts, largely in the form of trans- and cis-dichlorohexafluorobutene, 0.01 to 0.02 vol percent (10). This contaminant is one of the by-products of the manufacturing process. Since early 1965, it and other impurities have been largely eliminated from commercial halothane (54). The possible hepatotoxicity of contaminants is discussed in Part V of this report.

Halothane has a not unpleasant, oleaginous, sweetish odor. Mixtures of its vapor and oxygen are nonflammable in all proportions. However, in direct contact with open flame or spark, the compound is broken down to noxious products, such as phosgene. Halothane is compatible with all other anesthetics and with the commonly used carbon dioxide absorbents, such as Baralyme and soda lime. It causes deterioration of rubber and plastic materials; the vaporizers used for clinical administration, however, are made of resistant materials.

SOLUBILITY COEFFICIENTS, UPTAKE, DISTRIBUTION, AND ELIMINATION

Halothane has the following solubility coefficients at 36 C (Oswald): blood/gas, 2.3; brain/blood, 2.6; liver/blood, 2.6; kidney/blood, 1.6; muscle/blood, 3.5; and fat/blood, 60 (32). The blood/gas solubility coefficient is higher than those of anesthetic gases (ethylene, cyclopropane, and nitrous oxide) and lower than those of other anesthetic vapors (trichloroethylene, chloroform, methoxyflurane, and diethyl ether). Halothane is highly soluble in fat. Its oil/gas solubility coefficient (224) is exceeded only by those of chloroform (265), methoxyflurane (825), and trichloroethylene (960). Therefore, according to the principles that determine the uptake of inert gases by the body, during inhalation of halothane vapor equilibration between the inspired concentration and that in the body should be slower than with anesthetic gases and faster than with other anesthetic vapors.

Studies on uptake of halothane in man have confirmed this prediction. An estimated 10 to 12 hr are required to reach 95 percent equilibrium (58). In contrast, 95 percent equilibrium is reached in 10 min with cyclopropane (52,57). In clinical practice, induction of anesthesia with halothane can be achieved in a few minutes by using the principle of "overpressure," i.e., by administering the vapor in a concentration greater than that required for the maintenance of anesthesia. The vapor concentration is gradually lowered when surgical anesthesia is produced.

During the initial period of inhalation, halothane is carried principally to richly vascularized organs and tissues, the brain, heart, liver, kidneys, and muscles. Because the tissue/blood partition coefficients of these organs are relatively low, equilibration with blood occurs relatively quickly. As inhalation continues, more and more of the absorbed halothane is taken up by fat, which has a high tissue/blood solubility coefficient and a relatively poor blood supply. The slow and sustained uptake of halothane by fat accounts for the long period required to achieve equilibrium between the inspired mixture and the body as a whole. Complete equilibrium is seldom attained under clinical circumstances.

Elimination of halothane occurs almost completely via the lungs, following the reverse of the uptake pattern. Clearance of halothane from blood and lean tissues occurs promptly; approximately half the halothane in the body is cleared in 20 min. Patients usually recover from halothane anesthesia, to the point of responding to auditory stimuli, in 10 to 15 min. Complete clearance, however, requires many hours because of the high solubility in fat.

In the experimental animal, halothane labeled with isotopes (^{14}C or ^{36}Cl) undergoes metabolic degradation in the body to the extent of 3 to 10 percent, the major products being chloride, bromide, and trifluoracetic acid (68). These findings remain to be confirmed and the metabolic pathways defined.

ANESTHETIC CONCENTRATIONS AND TECHNIQUES OF ADMINISTRATION

Halothane is a potent anesthetic capable of producing anesthesia to any depth. Concentrations of halothane vapor required to induce and maintain anesthesia depend on several factors, including the physical status of the patient, the degree of sedation from preanesthetic medication, and the conjoint use of other anesthetics and adjunct drugs.

In unpremedicated dogs, the minimal anesthetic concentration in the alveolar air (defined as that necessary to prevent movement in response to a painful stimulus) is 0.87 percent (18). In healthy patients with adequate preanesthetic sedation, an inspired concentration of 2 to 3 percent of halothane in oxygen produces surgical anesthesia in 10 to 15 min. More rapid induction can be achieved with higher concentrations. This is possible because, unlike diethyl ether, halothane does not irritate the respiratory tract to cause cough or laryngospasm. For the same reason and because of its potency and relatively low solubility in blood, constant attention is required during induction with halothane to avoid inadvertent overdosage when using "overpressure."

One to two percent of halothane vapor in oxygen is required to maintain surgical anesthesia. The concomitant use of nitrous oxide reduces the required concentration of halothane in the inspired air. According to Saidman and Eger (56), the alveolar concentration of halothane required to prevent response to a standard stimulus is 0.76 percent when administered with oxygen and 0.2 percent when administered with nitrous oxide (70 to 75 percent) and oxygen.

A precision vaporizer is necessary for the safe administration of halothane because of its potency and its high vapor pressure at room temperature. Several such vaporizers have been designed. One type (33) embraces the "drawover" principle. A portion of the carrier gas (oxygen or a mixture of oxygen and another gaseous anesthetic, such as nitrous oxide) is diverted through a vaporizing chamber. The mixture laden with halothane vapor after dilution is then delivered to the anesthetic circuit. The proportion of gas diverted through the vaporizing chamber can be controlled. In addition, a thermocompensatory mechanism is provided so that changes in ambient temperature over a wide range will not alter the concentration of halothane vapor delivered. In another type of vaporizer (39), the carrier gas (oxygen) is bubbled through liquid halothane. The effluent mixture is fully saturated with halothane vapor. The concentration of halothane vapor delivered from the vaporizer can be calculated from the temperature of the liquid halothane and the vapor pressure of halothane at that temperature. Dilution with oxygen or a mixture of oxygen and other anesthetics in the breathing circuit gives the desired anesthetic concentration. In both systems, the halothane is vaporized outside the anesthetic circuit. The concentration of the vapor delivered to the circuit is independent of the patient's ventilatory activity.

Halothane may be administered by any of the commonly used anesthetic systems, varying from nonrebreathing to closed rebreathing techniques. In the nonrebreathing method, the inspired concentration of halothane equals the concentration delivered from the anesthetic apparatus. With an increasing proportion of rebreathing, the inspired concentration is proportionally lower and less predictable than that delivered from the anesthetic machine. The common practice is to use a semiclosed system with a total gas flow varying from 3 to 6 liters/min and an efficient carbon dioxide absorber in the rebreathing circuit. In the completely closed rebreathing technique, which is rarely used, the amount of halothane vapor added to the anesthetic circuit may exceed the uptake, resulting in an increasing halothane concentration. In those circumstances, constant monitoring of the inspired halothane concentration with such devices as an infrared or ultraviolet analyzer is desirable.

EFFECTS ON PHYSIOLOGIC SYSTEMS

Nervous System

The effect of halothane on the central nervous system in producing anesthesia is probably the same as that of other general anesthetics (14). Anesthetics depress the secondary afferent systems, i.e., the reticular activating system of the brainstem, to reduce the afferent input to the cerebral cortex. Halothane also depresses subcortical structures that regulate somatic and visceral functions.

The electroencephalogram during halothane anesthesia shows characteristic changes that correlate with increasing depth of anesthesia (22). Loss of consciousness is associated with the disappearance of alpha rhythm. The primary pattern during light anesthesia is a fast rhythm

(15 to 26 cycles/sec) with a low voltage (10 to 25 μv). With increasing depth of anesthesia the fast rhythm and low voltage gradually change to slow rhythm (2 to 3 cycles/sec) and high voltage (100 to 300 μv). Periods of electrical silence (burst suppression) then occur, interspersed with slow activity of reduced voltage. Complete absence of cortical activity has been observed during profound anesthesia. In general, these electroencephalographic changes are similar to those associated with other potent anesthetics.

Halothane appears to sensitize the peripheral mechanoreceptors thus far examined, including the pulmonary stretch receptors and the carotid baroreceptors (6,9,71). The stimulus threshold for these receptors is decreased and the frequency of discharge in response to a given physiologic stimulus is increased. The possible significance of this action of halothane in terms of neural regulation of respiration and circulation will be discussed later.

Halothane, like other potent anesthetics, depresses somatic reflexes (44). It does not appear to interfere with neuromuscular transmission in vivo (44,70). Therefore, skeletal muscle relaxation is produced through an action on the central nervous system, but only during deep anesthesia. However, the neuromuscular blockade of d-tubocurarine is potentiated by halothane (70).

Cerebral oxygen consumption is reduced by 15 percent during moderate depths of anesthesia with halothane, but that is partly explained on the basis of lowered body temperature (11). Cerebral blood flow increases (51 ml/100 g-min) in the face of a reduced arterial pressure, indicating cerebral vasodilation (cerebrovascular resistance, 1.1 mm Hg/ml/100 g-min) (74). The response of cerebral vessels to changes in carbon dioxide tension remains intact: vasoconstriction occurs during hypocapnia and vasodilation with hypercapnia. However, cerebral hypoxia has not been demonstrated during hypocapnia produced by hyperventilation, a common clinical practice (11). Cerebrospinal fluid pressure increases during halothane anesthesia, probably as a result of cerebral vasodilation (23,36).

Respiratory System

Halothane does not irritate the respiratory tract; during halothane anesthesia, mucous secretion is minimal and the bronchial muscles are relaxed.

Halothane is a respiratory depressant; it reduces the respiratory amplitude and slightly increases the rate. The increase in respiratory rate is probably in part the result of sensitization of the pulmonary stretch receptors (45,71).

In dogs, arterial carbon dioxide tension remains within normal limits when alveolar halothane concentration is 0.7 percent or lower. Above this concentration the arterial carbon dioxide tension rises linearly with increasing depth of anesthesia (38). Similarly, in man, during halothane anesthesia (1 to 3 percent inspired concentration) with spontaneous respiration, the alveolar carbon dioxide tension is increased (15,16). Both in animals and in man, the ventilatory response to a carbon dioxide challenge decreases in proportion to increasing depth of anesthesia (16,21,45,63).

Circulatory System

Halothane depresses cardiovascular functions. With a moderate depth of anesthesia, bradycardia, hypotension, and reduced cardiac output are regularly observed. These effects may be explained in part by a direct depressant action of halothane on the heart and blood vessels. The central action of halothane appears to play an important role in that similar circulatory depression can be produced when the distribution of halothane is limited to the head with perfusion techniques (51).

In experimental animals and in man, halothane depresses myocardial contractility (34,41,64). Peripheral vasodilation (an increase in blood flow in the skin and muscles) has been observed in man with the venous occlusion plethysmographic technique. The response of peripheral vessels to intra-arterially infused norepinephrine is reduced (7). In the mesoappendiceal microvessels of the rat, vasomotion is maintained during light to moderate halothane anesthesia (1 to 2 percent inspired concentration). Blood flow in the capillary bed, as estimated by direct observation, remains adequate. The reactivity of precapillaries to topically applied epinephrine appears enhanced. However, during deeper anesthesia (3 percent inspired concentration), vasomotion, blood flow, and epinephrine reactivity are depressed (2).

Circulatory homeostatic compensation is notably absent during halothane anesthesia. Barostatic reflexes are markedly depressed (43,51), although it has been suggested that sensitization of baroreceptors may contribute to the hypotensive action of halothane (6). Plasma concentrations of epinephrine and norepinephrine remain unchanged (50).

Ventricular arrhythmias may occur, resulting mostly from surgical manipulation during light anesthesia or from hypercapnia. Halothane sensitizes the heart to the arrhythmic action of catecholamines. In animals, intravenous administration of epinephrine during halothane anesthesia may result in ventricular tachycardia or fibrillation (53). However, in man, the use of epinephrine during halothane anesthesia is apparently safe if the dose of epinephrine is limited (not exceeding 10 ml of 1:100,000 solution in any given 10 min nor 30 ml/hr) and if precautions are taken to ensure adequate pulmonary ventilation (31). The use of vasopressors other than catecholamines, such as phenylephrine, ephedrine, etc., also in limited dose, is not accompanied by serious arrhythmias.

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Liver and Kidneys

In man, halothane significantly reduces the splanchnic blood flow (mean reduction, 25 percent) without changing splanchnic vascular resistance. The decrease in splanchnic blood flow is presumably the result of reduced arterial pressure. Hepatic oxygen consumption remains unchanged with a slight decrease in hepatic venous oxygen tension (from a mean of 53 to 47 mm Hg). However, evidence of tissue hypoxia, as estimated by production of "excess" lactate, has not been observed. Addition of carbon dioxide to the inspired mixture restores the splanchnic blood flow to control levels by producing vasodilation (20,49).

In dogs and in man, halothane decreases renal function. Glomerular filtration, renal plasma flow, urine flow, and sodium and chloride clearance all decrease significantly but are readily reversible on recovery from anesthesia (8,37). It is assumed that these changes are correlated with those of systemic hemodynamics, i.e., decreases in cardiac output and arterial pressure. Furthermore, the decrease in urine volume and sodium excretion may be reversed by the prophylactic administration of saline or mannitol (37).

Possible hepatotoxic effects of halothane have been extensively studied in a variety of animal species, including mice, rats, rabbits, guinea pigs, dogs, and monkeys. In contrast to chloroform, which produces liver necrosis with regularity, halothane does not cause liver necrosis after single or repeated administrations to these animals (29). Experiments have also been performed on protein-deficient mice. Halothane did not cause demonstrable pathologic changes in the liver (73). In rats and dogs, administration of halothane with a hypoxic or hypercapnic mixture also failed to cause liver necrosis (26,27,40). However, granular and fatty degeneration of the liver has been observed in mice, rats, guinea pigs, rabbits, and dogs (3,17,25,30,46,60,67).

The effect of halothane on liver function has been examined in man and compared with other commonly used anesthetics in limited series. The results are discussed in Chapter I-3.

Digestive System

Halothane decreases salivary and mucous glandular secretion. It relaxes the smooth muscle of the gastrointestinal tract and inhibits motility. Recovery occurs when halothane is withdrawn (35).

The incidence of nausea and vomiting after halothane anesthesia is significantly lower than after anesthesia with other agents. In large series of cases, the reported incidence varied from 2 to 10 percent. According to Bellville et al. (5), the incidence of postoperative nausea and vomiting was 27 percent with cyclopropane, 16 percent with diethyl ether, and 13 percent with thiopental-nitrous oxide.

Metabolism

In man given morphine or barbiturate and scopolamine for premedication, oxygen uptake falls to 72 to 87 percent of predicted basal values during halothane anesthesia (1.3 to 1.9 percent inspired concentration in mixture of 75 percent nitrous oxide and 25 percent oxygen) (62). The reduction in oxygen uptake is accompanied by considerable decreases in cardiac output and arterial pressure. When administered alone and without premedication, halothane (0.7 to 1 percent expired concentration) does not significantly alter oxygen uptake compared with predicted basal values (66). However, a decrease in oxygen uptake occurs if the body temperature is lowered significantly. The reduction in oxygen uptake observed in the first report is assumed to be attributable to premedicants and circulatory depression. A decrease in tissue perfusion may result in an oxygen debt to be repaid during recovery from anesthesia (61).

The influence of halothane on oxygen consumption in tissue slices in vitro has been studied (28). Halothane in concentrations of 1 and 2 percent appears to decrease oxygen consumption in rat brain, heart, and liver. For reasons unknown, the depressant effect on brain slices is not reversible. Anaerobic glycolysis in brain homogenates was not affected by halothane in concentrations (5 percent) that had a marked effect on oxygen consumption.

In the dog, halothane reduced blood glucose levels significantly (19 mg percent below the control). The transfer of glucose but not fructose from plasma to tissues is impeded; the half-time of the glucose tolerance test is prolonged (39 min), compared with that of animals in a control group (24 min) (24).

CLINICAL USE OF HALOTHANE

Since its introduction to clinical practice, halothane has received increasing acceptance. In the vast majority of cases, halothane is being administered in conjunction with a thiobarbiturate, nitrous oxide, and a neuromuscular blocking agent when muscle relaxation is required. With this balanced technique it is possible to provide a smooth course of light surgical anesthesia with a relatively low concentration of halothane.

The important advantages of halothane are:

Nonflammability, which abolishes the risk of anesthetic explosion from static discharge and the risk in surgical procedures requiring the use of electrical equipment. Anesthetic fires and explosions, although not officially reportable, occur once in about 100,000 administrations with an estimated death rate of one in 2 to 3 million administrations. This would mean approximately five to 10 deaths per year in the United States.

Absence of respiratory tract irritation, which permits a nonstressful, rapid induction of anesthesia. Major respiratory complications, such as laryngospasm, "expiratory spasm," and bronchospasm, occur rarely during this critical period. In addition, halothane is effective in the amelioration of bronchospasm because it relaxes bronchial muscle. Halothane is therefore used therapeutically in asthmatic crises, particularly bronchospasm occurring during anesthesia.

Relatively uneventful and rapid recovery from anesthesia, with a low incidence of postanesthetic nausea and vomiting. This attribute may be important after certain surgical procedures in terms of preventing wound dehiscence and disturbance of fluid and electrolyte balance.

Absence of significant metabolic effect. Although the clinical significance of metabolic derangements observed during anesthesia with some other agents is ill-defined, it would appear that the benign effects of halothane may contribute to the general well-being of the surgical patient.

However, halothane is not an ideal anesthetic;* it does have undesirable pharmacologic properties. But in clinical use these disadvantages can be minimized by practice and by techniques developed through proper training and experience.

Circulatory depression. Shortly after the introduction of halothane into clinical use, a number of reports called attention to the hazards of overdosage and circulatory collapse. Such reports have largely ceased to appear, because of increasing experience and development of knowledge concerning the physical properties of halothane, uptake by the human body, anesthetic concentrations required, and the use of precision vaporizers. Depression of cardiovascular function is still evident when halothane is administered as the sole anesthetic, especially when used to provide muscular relaxation. In clinical practice, combined use with other agents, such as nitrous oxide and thiobarbiturate, and neuromuscular blocking agents, to a large extent minimizes the cardiovascular depression.

Questions have also been raised as to the physiologic significance of minimal or even moderate decreases in cardiac output and arterial pressure. Where measurements have been made in man, e.g., cerebral and splanchnic circulation and metabolism, moderate hypotension and decrease in blood flow to these areas in the absence of vasoconstriction are not associated with a significant reduction in tissue oxygen consumption or with any evidence of tissue hypoxia.

Halothane has been used to produce deliberate hypotension. The absence of sympathoadrenal activation during halothane anesthesia and the possible deleterious effects of prolonged peripheral vasoconstriction, as shown by studies on shock, place halothane in an advantageous position in the management of patients in impending shock or shock, provided, of course, that appropriate steps are taken to correct blood-volume deficiency.

Respiratory depression. This effect is not unique in anesthesia. With current concepts and practices of anesthesia, and with the increased training and ability of the anesthetist to provide adequate ventilation during anesthesia, respiratory depression due to halothane should not be considered a practical disadvantage.

The smooth-muscle relaxing action of halothane on the gravid uterus (19, 69) has been considered by some as disadvantageous in the management of obstetric patients. Impeding of the birth process and increased postpartum hemorrhage could result from such uterine relaxation. Thus, it has been recommended that halothane not be used in obstetrics except when uterine relaxation is required (12). This point is debatable. Reports of experience in large series of cases have failed to show that the incidence of postpartum hemorrhage is higher with halothane anesthesia, except when operative obstetric procedures were involved (13,72).

Another action of halothane, namely, increase in intracranial pressure, has been interpreted as disadvantageous in the management of anesthesia for neurosurgical procedures. It has not been proved that this increase in intracranial pressure is indeed deleterious. The advantages of halothane mentioned above have made it an agent of choice in the minds of those responsible for the anesthetic care of these patients.

The possible hepatotoxic effect of halothane in man is one of the primary subjects studied by the Subcommittee on the National Halothane Study.

*An ideal anesthetic, according to the views of Seevers and Waters (59), Beecher and Ford (4), and Artusio and van Poznak (1), should be inexpensive to produce, pure, stable, and nonflammable; it should have low solubility coefficients in blood and tissues and an intermediate potency; it should not depress respiration or circulation, or cause major disturbance of other physiologic functions; it should provide adequate muscular relaxation; and the induction of anesthesia should be swift and pleasant, and recovery should be free from ill effects of the anesthetic.

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CHAPTER I-3. HEPATIC EFFECTS OF HALOTHANE REVIEW OF THE LITERATURE

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Soon after halothane was introduced into clinical practice, a number of publications appeared describing experiences with it. The reports described series ranging from fewer than 100 to thousands of cases, and were primarily concerned with anesthetic techniques and the patients' responses during and after anesthesia. Few specifically mentioned the possible hepatotoxic effects of halothane.

Before 1960, Little et al. (55) studied hepatic function in 10 patients before and after halothane anesthesia and compared the results with those in patients anesthetized with cyclopropane or diethyl ether. Transient hepatic dysfunction was observed, but there was no significant difference among these anesthetics. Stephen et al. (77) used the sulfobromophthalein (Bromsulphalein, BSP) retention test in 51 patients anesthetized with halothane and found no difference between this group and those anesthetized with other agents. Three fatal cases of hepatic necrosis after halothane anesthesia were reported - one after aortic valvuloplasty in a patient with severe congestive heart failure (16), one after cholecystectomy complicated by episodes of cardiovascular depression during anesthesia (86), and one after an uncomplicated inguinal herniorrhaphy (87). These authors suspected halothane of contributing to the deaths, but obviously other factors could have played a role. Three cases of nonfatal postoperative hepatic complications after halothane anesthesia were also reported, but detailed information on hepatic function was not available (5,16).

A number of case reports of hepatic necrosis after halothane anesthesia appeared late in 1962 and early in 1963 (14,15,54,78,80). These reports raised the question of the safety of this anesthetic agent and served as the impetus for the National Halothane Study. Since then, additional cases, both fatal and nonfatal, have been reported and many have cast suspicion on or implicated halothane as a hepatotoxin. Such a contention could hardly have been proved because of the multitude of factors leading to hepatic necrosis in patients undergoing operation. While the National Halothane Study was in progress, a number of retrospective surveys and prospective studies were carried out in an attempt to prove or disprove a causal relationship between halothane and hepatic necrosis and to estimate the incidence of postoperative hepatic complication as related to various anesthetic agents. The following section summarizes the pertinent literature to January 1966.

RETROSPECTIVE STUDIES

Retrospective studies of the incidence of postoperative hepatic necrosis vary considerably in the methods and case material used. Table 1 summarizes the total number of cases thus studied and the frequency of use of halothane and other anesthetics associated with fatal and nonfatal hepatic necrosis. Data were obtained from anesthesia registers, hospital charts, and necropsy records. In some the total number of cases was approximate. Fatal cases were gathered from among those patients who died from 4 weeks to 4 months following anesthesia, although in a number of reports the time was not recorded. Performance of necropsy varied from 65 to 90 percent.

In Table 1 the cases listed under the heading "Nonhalothane" include those involving anesthesia with all commonly used agents: thiopental-nitrous oxide, cyclopropane, diethyl ether, and other halogenated agents (trichloroethylene, methoxyflurane, and fluoroxene). Most authors excluded, or considered separately, those cases with preoperative hepatic disease. Detailed description of the liver pathology was not provided in all reports. Thus, the incidence of hepatic necrosis after anesthesia as estimated from these data must be viewed with caution. It is unlikely that a significant number of patients who died of massive hepatic necrosis were overlooked in these surveys. Rather, the incidence of massive hepatic necrosis may have been overestimated. In the series of Slater et al. (75) and Gingrich and Virtue (33), the extent of hepatic damage found at necropsy varied from fatty infiltration to focal necrosis or massive necrosis.

Additional pertinent information may be gathered from a few of these reports. Keéri-Szántó and Lafleur (48) found that, of approximately 100 patients with pre-existing serious hepatic disease, seven died of hepatic complications. Of these, two were given halothane anesthesia, but that agent was administered to approximately 52 percent of the patients in this selected group. In another series (46), 185 patients with cirrhosis of the liver underwent portal-systemic venous anastomosis. Halothane anesthesia was administered to 44 patients and other agents to 141. The over-all mortality rate was 10.8 percent, but there was no significant difference in mortality between the two groups. Similar results were reported by Benke (8) in a series of 130 patients with pre-existing jaundice of diverse origin, 25 of whom were given halothane. In addition, Dawson et al. (25) analyzed

TABLE 1.--RETROSPECTIVE STUDIES IN THE LITERATURE COMPARING THE HEPATIC EFFECTS OF HALOTHANE AND OTHER ANESTHETIC AGENTS

Reference	Period of survey	Total no. cases	Halothane		Nonhalothane		Necropsy rate, (%)
			No. administrations	No. cases hepatic necrosis	No. administrations	No. cases hepatic necrosis	
48	1959-1962 (48 months)	50,000*	35,000*	6	15,000*	1	---
2	1960-1963 (38 months)	36,000*	13,024	0	23,000*	1	---
75	1959-1962 (48 months)	46,923	14,685	3	32,238	7	65
22	1959-1963 (48 months)	13,176	6,509	0	6,667	0	---
64	1960-1962 (36 months)	26,844	16,684	0	10,160(2712)	1 (0)	74.7
38	1960-1963 (48 months)	48,311	21,461	1	26,850	2	---
65	1958-1962 (60 months)	22,701	6,618	0	16,083	0	88
33	1953-1963 (10 years)	24,112	3,073	1	21,039(717)	5 (0)	90
27	1956-1963 (8 years)	102,342	20,232	1	82,110	0	75
Total and incidence of hepatic necrosis		370,409	137,286	12 1:11,440	233,147(3429)	17 1:13,715	

*Estimated

Numbers in parentheses indicate anesthesia with trichloroethylene, methoxyflurane, or fluoroxene, as mentioned in original report.

their experience with operations on the biliary tract. In 1958, diethyl ether was used in 925 patients; in 1962, halothane was used in 749. About 2 percent of patients in both groups revealed preoperative evidence of hepatocellular disease. One patient in each group died of hepatic failure. Analysis of postoperative hepatobiliary complications or mortality, from known or unknown causes, revealed no significant difference between the groups. Thus, from these experiences it would appear that neither pre-existing hepatic disease nor operation on the biliary tract contraindicates the use of halothane. Data from the National Halothane Study lend further support to this contention (see Chapters III-1 and IV-3).

In addition to the aforementioned studies of postoperative death, Mushin et al. (64) and Henderson and Gordon (38) examined the frequency of postoperative hepatic dysfunction as indicated by abnormal hepatic function tests or jaundice. It was assumed that major hepatic damage occurring while the patient was in the hospital would have been observed by the attending clinician and that appropriate tests would have been performed. Data were obtained from the records of the biochemical laboratory. Reference to the clinical charts permitted analysis of anesthetic or surgical factors. Mushin et al. concluded from their survey of 26,844 cases that halothane differs little from other anesthetics in its effect on the liver. Again, in patients with pre-existing liver disease, halothane did not appear to result in greater degrees of hepatic dysfunction than other anesthetics. Henderson and Gordon (38) found that the incidence of postoperative jaundice (defined as a serum bilirubin greater than 1.5 van den Bergh units, preoperative jaundice being excluded) increased from 1.1 per 1000 during the period 1953-1956 to 4.2 per 1000 during the period 1960-1963. These authors attributed the increase to the changing character of surgical practice and to more frequent use of blood transfusions and new therapeutic agents. During 1960-1963, however, when halothane was compared with other anesthetics, there was no difference in abnormal hepatic function tests, the incidence being 4.1 and 4.2 per 1000 after halothane and other agents, respectively. Although retrospective surveys of this nature do not ensure identification of all cases of postoperative hepatic dysfunction, it is reasonably certain that most cases with

major hepatic complications must have been discovered.

Two other retrospective studies are of interest in that they indicate the relative infrequency of massive hepatic necrosis associated with anesthesia and operation. Caravati and Wootton (17) examined all necropsy records in three community hospitals during the 16-year period 1946-1961. Total hospital admissions numbered 662,252. Massive hepatic necrosis was found in nine of 9960 patients who came to necropsy. Only three of these had been subjected to anesthesia and operation soon before the onset of hepatic complications and death. None of these patients received halothane. Rodgers et al. (69) reviewed all necropsy records of a large city hospital during the 10½-year period 1953-1963. Eighteen instances of massive hepatic necrosis were found among 11,341 necropsies. Six of the 18 patients had undergone operation. The primary anesthetics administered were: cyclopropane, three cases; diethyl ether and cyclopropane, one case; and halothane, one case; the remaining patient was operated on without general anesthesia. Clinical, laboratory, and necropsy findings of these cases are set forth in Tables 3 and 4. Although in some the etiologic factor was not ascertained, it appeared that viral hepatitis, prolonged hypotension treated with vasopressor drugs, septicemia, and reactions to therapeutic agents were causative in most instances. Anesthesia did not seem to play a role, no matter the agent. The total number of administrations of general anesthesia during the period of survey was not mentioned in either of these reports, but Rodgers et al. estimated that, since 1958, 3000 to 4000 patients per year had been anesthetized with halothane in their hospital.

Another form of retrospective survey was carried out by Green and Mungavin (35), who asked practicing anesthetists in England for information on cases of hepatic complications suspected of having occurred after halothane anesthesia. More than 1000 replies yielded 47 cases, of which 16 were fatalities. It is of interest that, in 10 of the 16 fatal cases, the cause of the hepatic complication was "indeterminate." The value of this type of survey is questionable in terms of incidence of complication and comparison with other anesthetics. There was no assurance that all pertinent cases were known or reported, and the frequency of use of the anesthetic was not indicated. These authors also searched for cases of fatal hepatic necrosis among necropsy records of six teaching hospitals. The survey was carried out for the years 1956 to 1963 and covered a cumulative total of 28 years of experience. There were 18 cases associated with halothane anesthesia and 14 cases in which halothane was not used. Again, the total number of administrations of general anesthesia was not available, although it was estimated that 60 percent of the patients had received halothane.

A number of reports dealt with halothane anesthesia alone and cited the incidence of postoperative hepatic complications or their absence (11,31,32,39,41,44,56,66,71,77,88). The numbers of cases in the reports ranged from 400 to 12,000. The incidence of postoperative jaundice ranged from 33 in 2700 cases (39) to none in 10,000 to 12,000 (31,66,88). It seems certain that there was little uniformity in the method of case searching; nor can it be assumed that etiologic factors other than anesthesia were not involved. Nevertheless, the report of Bentel (11) is of interest. Over a period of 4 years, Bentel regularly (approximately 20 times per week) used halothane, pentolinium (Ansolysen), and posture to induce hypotension (systolic arterial pressure, 60 to 70 mm Hg) for the performance of various surgical procedures. There were only three cases of jaundice that developed 6 months to 1 year after operation, presumably from causes other than anesthesia.

From the large numbers of cases in the retrospective surveys, it may be concluded that massive hepatic necrosis after anesthesia and operation is indeed rare. The exact incidence cannot be ascertained from these data, but it appears that halothane differs little from other anesthetic agents, even if anesthesia were considered a contributing etiologic factor. From limited experience it may be stated also that halothane is comparable with, and possibly superior to, other anesthetic agents in its safety in the management of patients with hepatic disease or for operation on the biliary tract.

PROSPECTIVE STUDIES

Retrospective studies only partially answer the question of whether postoperative hepatic necrosis is associated with halothane more frequently than with other anesthetics, and may provide estimates of the incidence of fatal and nonfatal hepatic complications. However, the very nature of such studies leaves much to be desired. In institutions with large surgical caseloads, it is unlikely that close scrutiny and adequate postoperative examination are afforded all patients. It may also reasonably be assumed that the frequency with which a complication is found is directly related to the index of suspicion. Thus, bias on the part of the observer cannot be discounted. Although cases of serious and fatal hepatic necrosis are not likely to be missed in retrospective studies, the incidence of milder forms of hepatic dysfunction after halothane or other anesthetic agents would be generally unknown. Furthermore, choice of anesthetic agent may have been dictated not only by clinical circumstances but by the personal preference of the anesthetist. These variables are important in the final results, but are not apparent in statistical analyses such as those described above.

TABLE 2.--PROSPECTIVE STUDIES IN THE LITERATURE COMPARING THE HEPATIC EFFECTS OF HALOTHANE AND OTHER ANESTHETIC AGENTS

Reference	Method of patient selection	Liver function tests used	Time of tests	No. of cases		Results or conclusions
				Halothane	Others	
77	--	BSP retention (45 min)	Postoperatively, 24 hr and 5 days	51	51	Comparable results in both groups
55	--	Cholinesterase, cholesterol, cholesterol esterification, alkaline phosphatase, bilirubin, cephalin flocculation	Preoperatively; postoperatively, days 2 and 7	10	20	Comparable minor changes after anesthesia
36	Paired	Bilirubin, SGOT, SGPT, BSP retention (45 min)	Preoperatively; postoperatively, 24 hr	27	30*	Minor changes in hepatic function after anesthesia attributed to operation rather than to anesthesia. No significant difference between halothane and chloroform
70	Random	SGPT	Preoperatively; postoperatively, 24 hr	140	140	6 patients in each group had postoperative SGPT higher than 39; study in progress
7	--	OCT	Preoperatively; postoperatively, 2, 4, 6, 8 days	13	3	All values within normal limits
22	Random	SGPT	Preoperatively; postoperatively, 2 or 6 days	164	104	No significant difference between preoperative or postoperative values
23	--	Liver biopsy, OCT	Beginning and end of operation	10	6	No change observed in liver biopsy; all OCT values within normal limit
76	--	SGOT, SGPT, LDH, MDH	Preoperatively; during operation; postoperatively, 24 hr	19	11	No abnormal values observed
50	Matched series	Urobilinogen, cholinesterase, SGPT	Preoperatively; postoperatively, 6 and 30 hr SGPT only	84	84	Halothane group not different from nonhalothane groups
51	Matched series	SGPT	Preoperatively; postoperatively, 6 and 30 hr	50	50 +50*	No evidence of hepatic dysfunction after halothane or chloroform
67	--	BSP retention prothrombin time, guanase, OCT	Preoperatively and postoperatively, 1 and 5 days; preoperatively and postoperatively 1 and 3 days	21	21	BSP retention elevated postoperatively; no significant difference between halothane and nonhalothane series

Table 2 (Cont'd)

Reference	Method of patient selection	Liver function tests used	Time of tests	No. of cases		Results or conclusions
				Halothane	Other	
42	Paired	Bilirubin, SGOT, ICD	Preoperatively; postoperatively, 1, 2, 3 days	46	30 36**	1 patient (halothane) showed elevated SGOT (1260) and ICD (6260); no significant abnormalities in remaining patients
27	Random	ICD	Preoperatively; postoperatively, 1 and 4 days	139	84	No significant difference between the two groups

Abbreviations: SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase; OCT, ornithine carbamyl transferase; ICD, isocitric dehydrogenase; LDH, lactic dehydrogenase; and MDH, malic dehydrogenase.

*Chloroform.

**Regional anesthesia.

A well-designed prospective study may eliminate some of these discrepancies, but certain criteria must be considered. Depending on the incidence of postoperative hepatic complications, the size of the sample must be adequate to permit statistical analysis. Patients must be selected on a broad basis, with respect to age, sex, physical status, and type of operation. If one anesthetic agent is to be compared with another without bias, patients must be randomly assigned to each group. Appropriate laboratory tests must be performed at the proper time to detect hepatic dysfunction. It may be difficult to execute such a study properly because of practical and ethical problems.

Table 2 summarizes the results of published prospective studies comparing the effect of halothane and other anesthetic agents on hepatic functions. These studies vary considerably in the size of samples, the liver function tests applied, and the time of application of these tests postoperatively. With few exceptions, the samples were small. Only three studies randomly assigned the anesthetic agent to be administered. In some, postanesthetic alterations in hepatic function were not followed beyond 30 hr. Despite these limitations, the general conclusion has been that there is no significant difference among halothane and other agents in their effects on the liver. Transient abnormalities, presumably attributable to the operation, were found with equal frequency.

A number of reports have dealt with the effect of halothane alone. Lorentz and Henneberg (57) measured serum lactic dehydrogenase in 16 patients 24 and 48 hr after halothane anesthesia for major surgical procedures; there was no change of significance. Tracy and Heyman (81), Urso et al, (83), and Pichlmayr and Pichlmayr (66) studied hepatic functions in a total of 134 surgical patients who were anesthetized with halothane. Hepatic function tests included sulfobromophthalein retention, serum transaminase levels, bilirubin concentration, flocculation, and alkaline phosphatase. Although transient abnormal values were observed in some patients, the role of pre-existing disease, concurrent drug therapy, and the operative procedure was unknown. No comparable series of cases with other anesthetic agents were available for comparison.

Keéri-Szántó (47) reported a prospective study involving 250 surgical patients anesthetized with halothane, methoxyflurane, or neuroleptanalgesic mixtures. He observed a greater intraoperative sulfobromophthalein retention with halothane than with methoxyflurane. In another 100 patients, the degree of abnormal BSP retention 5 days postoperatively was greater in those who received higher concentrations of halothane (2 percent) for induction than in those who received 1 percent of halothane. The possible significance of these results is obscure.

McReynolds et al. (61) compared halothane and chloroform in 763 patients; 548 patients received halothane and 215 chloroform. Distribution of patients according to age, physical status, and site of operation was approximately the same for both groups. The over-all mortality rate was 3.7 percent in the chloroform group and 2.7 percent in the halothane group, not significantly different from the total hospital death rate after administration of other anesthetic agents in the same institution. One patient with severe preexisting hepatic disease died with diffuse hepatic and kidney necrosis, 15 days after chloroform anesthesia and 22 days after halothane anesthesia for a previous operation. Three patients in each group incurred "minor" hepatic complications. The authors concluded that halothane and

chloroform are similar in clinical effect, usefulness, and safety.

CASE REPORTS

The service of the National Library of Medicine was requested to ensure complete coverage of the literature during the period 1963-1965. On the basis of its data-retrieval system and the sorting of a total of 350,000 references, a list of publications was compiled to include all papers pertaining to anesthesia, halothane, toxicologic reports, jaundice, hepatic disease, hepatitis, hepatic necrosis, and postoperative complications. In addition, the medical library of the Ayerst Laboratories kindly provided a complete bibliography on halothane for 1956 to 1965. These lists were screened and all pertinent references perused for case histories of hepatic complications after anesthesia and operation.

This process yielded 132 cases of postoperative death due to hepatic necrosis or associated with some degree of pathologic change in the liver but not necessarily massive necrosis. An additional 124 cases were selected in which evidence of postoperative hepatic dysfunction was presented. This evidence included clinical jaundice, abnormal hepatic function tests, and biopsies. Relevant clinical histories and laboratory and pathologic findings, where available, are presented in Tables 3 and 4 (fatal cases) and 5 and 6 (nonfatal cases). Most but not all of the fatal cases mentioned in the section on retrospective studies are included. In the retrospective studies of Keéri-Szántó and Lafleur (48), Allen and Metcalf (2), and Henderson and Gordon (38), 11 patients incurred hepatic necrosis; of these, seven had received halothane anesthesia. The survey of Green and Mungavin (35) of six hospitals in England yielded 32 cases of hepatic necrosis, 18 associated with halothane and 14 with other agents. None of these 43 cases is included in Tables 3 and 4, because of lack of details.

Slater et al. (75) presented histories of two of their 10 patients in whom necropsy revealed hepatic necrosis of various degrees of severity. A subsequent publication by the same authors (29) provided additional information on nine patients who showed evidence of acute parenchymatous hepatic disease at necrospy. Overlaps in reporting are apparent in these publications, as well as in those by Virtue and Payne (86), Gingrich and Virtue (33), Lindenbaum and Leifer (54), and Blackburn et al. (13). Obvious duplications are omitted from Tables 3 through 6.

The preponderance (in Tables 3 through 6) of cases associated with halothane reflected the current interest in this problem. The degree of suspicion that each author held certainly played an important role in these reports. Thus, the majority of cases involving anesthetic agents other than halothane were reported in connection with retrospective surveys when the total experience in a given institution was scrutinized. When this was done, the incidence of hepatic necrosis or dysfunction associated with halothane usually did not differ significantly from that associated with other agents (cf. the section on retrospective studies and Table 1).

Case reports cited herein varied considerably in details of clinical histories, particularly regarding circulatory status during and after operation, transfusion, and concurrent drug therapy. Descriptions of pathologic changes in the liver were not always given in sufficient detail. For these reasons, no attempt will be made to discuss individual cases. Nevertheless, in a number of cases hepatic necrosis and dysfunction can probably be explained on the bases of pre-existing hepatic disease, such cardiovascular disturbances as congestive heart failure and shock, prolonged treatment with vasopressor drugs, and overwhelming infection. Because it is not possible to review all reported cases in the same manner as was done for the cases collected in the National Halothane Study, it would not be fruitful or justifiable to render an opinion concerning the probable cause(s) of hepatic necrosis in any of the reported cases. The possibility of coincidental viral infection was repeatedly mentioned, but this must remain conjectural, as shall be the contention of many other authors who implicated halothane.

Thus, it appears that, even with such a large series of patients who incurred postoperative hepatic damage, any conclusion based on case reports concerning the causal relationship between halothane and hepatic necrosis would be unwarranted. These reports cannot be taken to prove that halothane is or is not hepatotoxic.

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TABLE 3.--HEPATIC DAMAGE AFTER ANESTHESIA AND OPERATION--FATAL CASES IN THE LITERATURE (1958-1966), CLINICAL HISTORIES*

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
1	16	M 48	Chronic passive congestion	Aortic valvuloplasty	H (60) C (120)	Yes	Hypotension during operation	--	?	Hepatic failure 6
2	86	F 39	Jaundice	Cholecystectomy, choledochotomy	H	No	Hypotension and respiratory depression during operation	Penicillin streptomycin, erythromycin, tetracycline	--	Hepatic failure 11
3	87	M 35	None	Inguinal herniorrhaphy	H (60)	No	--	Penicillin, edrenoxyl, vitamin K	4	Hepatic failure 4
4	78	M 44	Alcoholism	(1) Skin graft, leg	H (30)	No	--	--		(24)
				(2) Thyroidectomy	H (180)	Yes		Penicillin, steroids	2	Hepatic failure 3
5	17	M 16	None	Appendectomy	Non-H	Yes	--	Penicillin, streptomycin, chloramphenicol, sulfamethoxypyridine, Furadantin	2	Hepatic failure 23
6	17	M 41	None	Lobectomy	Non-H	Yes (6 weeks previously)	--	Isoniazid, para-amino salicylic acid, pyrazinamide, streptomycin	14	Hepatic failure 23
7	17	M 69	None	Prostatic biopsy	Non-H	No	Septicemia	Sulfisoxazole	? 2	Septicemia 9
8	60	M 48	None	Laminectomy	Ch (300)	Yes	Hypotension during operation	Imipramine (preoperatively)	No jaundice	Sudden death; ? cardiac 2
9	61	M 72	Alcoholism, jaundice, enlarged liver	(1) --	H	--	--	--	--	(22)
				(2) --	Ch	--	--	--	Progressive	Hepatic failure 15
10	25	M 48	Cirrhosis	Cholecystectomy, choledochotomy	E	--	Transient hypotension during operation	Prochlorperazine	7	Hepatic failure 32
11	25	F 58	--	(1) Esophagoscopy	H	--	Atrial fibrillation	--		
				(2) Cholecystectomy, repair of diaphragmatic hernia	H	--	Dehiscence	Prochlorperazine	(25)	(28)
				(3) Wound repair	H	--	Dehiscence	--	(6)	(9)
				(4) Wound repair	H	--	--	--	2	Hepatic failure 5
12	25	F 74	--	Cholecystectomy, gastrostomy	E	Yes	--	Prochlorperazine	? 24	Leukemia 34
13	14	F 70	Abnormal hepatic function tests	Cholecystectomy, liver biopsy	H (170)	No	--	--	15	Hepatic failure 20
14	14	F 74	Episodes of dark urine and light-colored stools	Cholecystectomy, choledochotomy, liver biopsy	H (180)	No	Cholangitis, staphylococcal	Bunamiodyl, antibiotics	? 26	Hepatic failure 43
15	14	M 63	None	(1) Repair of retinal detachment	H (160)	No	None	--	---	
				(2) Same	H (150)	No	None	--	--	(72)
				(3) Same	H (165)	No	None	--	? 6	Hepatic failure 16

*H, halothane; N, nitrous oxide; C, cyclopropane; E, diethyl ether; V, divinyl ether; Ch, chloroform; M, methoxyflurane; Tr, trichloroethylene; and R, regional anesthesia.

Table 3 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
16	15	F 16	None	Repair lacerated wrist	H (280)	No	None	--	No jaundice	Hepatic failure 14
17	15	M 67	Alcoholism	(1) Plication of perforated duodenal ulcer	H (85)	No	None		--	(19)
				(2) Gastrectomy	H (285)	Yes	Hypotension	--	6	Hepatic failure 9
18	54	M 49	Alcoholism	(1) Plications of perforated duodenal ulcer	H (80)	No	None	--		(59)
				(2) Gastrectomy	M (235)	No	None	Neomycin, hydrocortisone, vitamin K	2	Hepatic failure 10
19	80	F 68	None	(1) Radical mastectomy	H (135)	Yes	None	--	--	(52)
				(2) Skin graft	H (30)	No	None	Tetracycline, prochlorperazine, isopropamide	11	(43)
				(3) Exploratory laparotomy	C	No	None	--	Progressive	Hepatic failure 17
20	80	F 62	None	Cholecystectomy, choledochotomy	H	No	None	Tetracylcine, novobiocin, promethazine	21	Hepatic failure 38
21	19	F 55	None	(1) D & C	H	No	None	--	(18)	(25)
				(2) Hysterectomy	H (90)	No	G.U. tract infection	Sulfadimidine	11	Hepatic failure 18
22	26	F 55	None	(1) Pelvic examination	H	No	None	--	--	(63)
				(2) Hysterectomy	H (125)	No	Wound infection	Penicillin, streptomycin, tetracycline	19	(56)
				(3) Radium implantation	H (10)	No	None	Neomycin, prednisone	Progressive	Hepatic failure 21
23	34	F 55	None	(1) Cholecystectomy, choledochotomy	H	No	Transection hepatic duct, reanastomosis	promethazine	17	(27)
				(2) Exploratory laparotomy	H	No	None	--	Continued	(10)
				(3) Exploratory laparotomy	Non-H	No	None	--	Continued	Hepatic failure 6
24	84	F 82	None	Colectomy, herniorrhaphy	H	Yes	None	Penicillin, streptomycin	5	Hepatic failure 7
25	6	F 68	None	(1) Radium implantation	H, Tr	No	None	--	(23)	(46)
				(2) Same	H, Tr	No	None	--	(16)	(39)
				(3) Same	H, Tr	No	None	--	2	? Hepatic failure 25
26	62	F 67	None	(1) Cholecystotomy	M (60)	No	None	Oxytetracycline	(23)	(26)
				(2) Keller's operation	H (90)	No	None	--	3	(6)
				(3) Choledochotomy	N	No	None	--	Continued	Hepatic failure 3
27	20	F 40	None	(1) Cervical biopsy	N	No	None	--		(28)
				(2) Radium implantation	H	No	None	--	(15)	(18)
				(3) Radical hysterectomy	H, R (140)	Yes	None	Neomycin, steroid	1	Hepatic failure 4
28	75	M 70	None	(1) Gastrectomy	C (240)	Yes	Hypothermia, hypotension	Norepinephrine infusion, prolonged	2	(9)
				(2) Exploratory laparotomy, colon resection	None	--	Moribund		Continued	? Shock 1

Table 3 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Trans-fusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
29	75	M 54	--	(1) Craniotomy	H (570)	Yes	Status epilepticus	Barbiturates, diphenyl-hydantoin	--	(23)
				(2) Craniotomy	H (330)	Yes	Transient hypotension during operation	Prochlorpera-zine	8	Hepatic failure 10
30	64	F 68	--	Reduction fractured tibia and fibula	H	Yes	--	Nitrofurantoin, oxytetracyc-line, phenindione, neomycin	Jaundice	? 54
31	64	F 52	--	(1) Sigmoidoscopy	H	No	--	Phthalylsulfa-thiazole, neomycin	(15)	(32)
				(2) Colectomy	Non-H	Yes	--	--	(1)	Hepatic failure 8
32	1	F 49	None	(1) Biopsy, vulva	H (65)	No	Cystitis	Azo-gantrisin	--	(57)
				(2) Vulvectomy	H (60)	Yes	None	Chloramphenicol	(22)	(35)
				(3) Inguinal node dissection	H (70)	Yes	None	Penicillin, streptomycin, neomycin, Solucortef, Konakion	2	Hepatic failure 6
33	18	F 56	None	(1) Sigmoidoscopy	H	No	None	--		(26)
				(2) Colostomy	H (	No	None	Neomycin, promethazine	(11)	(17)
				(3) Colectomy	H (165)	Yes	None	Tetracycline "trichloryl"	5	Hepatic failure 11
34	53	F 68	--	Cystectomy	H	--	--	--	Not stated	Renal failure 14
35	9	F 75	None	Gastrectomy, pyloroplasty	C	Yes	--	--	5	Pulmonary infarction 8
36	9	F 74	None	Hemicolectomy	C	Yes	None	--	No jaundice	Not stated 21
37	28	M 54	Alcoholism, cirrhosis	(1) Amputation, foot	R	No	None	Oral anti-diabetic drugs, tetracycline, chloramphenicol	--	(23)
				(2) Same	R	No	None	--	--	(16)
				(3) Laminectomy	H (225)	Yes	None	Aureomycin, chloramphenicol	2	Hepatic failure 8
38	13	F 59	None	Tonsillectomy	H (90)	No	Hypotension	--	? 14	Hepatic failure 40
39	13	F 23	Pre-eclamp-sia, mild	Cholecystectomy	H (105)	No	None	Antibiotics	?	Hepatic failure 12
40	13	F 39	None	(1) Breast biopsy	H (75)	No	None	--	--	(17)
				(2) Radical mastectomy	H (180)	No	Convulsion, postopera-tively	Penicillin, tetracycline, chloramphenicol	? 6	Hepatic failure 6
41	13	M 73	None	(1) Cystoscopy	H (15)	No	None	--	--	(40)
				(2) Prostatectomy	R (80)	No	None	--	--	(36)
				(3) Cystoscopy	H (30)	No	None	--	--	(12)
				(4) Excision renal cyst	H (75)	No	None	--	1	Hepatic failure 8
42	10	F 54	None	(1) Carotid arte-riogram	H (75)	No	None	Diatrizoate		
				(2) Craniotomy	H (270)	Yes	None			
				(3) Carotid arte-riogram	H (75)	No	None	Diatrizoate	5	
				(4) Arteriogram and craniotomy	H (270)	Yes	None	Urografin	8	? 7 mos.

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Table 3 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
43	69	F 53	Jaundice	Exploratory laparotomy	C	Yes (4 mos. preoperatively)	--	Isoniazid, para-aminosalicylic acid, sulfisoxazole, diphenylhydantoin, primidone	Continued	--
44	69	M 66	Alcoholism	Debridement and skin grafts x 5	E, C, N	Yes	--	--	2 months	-- 69
45	69	F 69	Jaundice	Exploratory laparotomy	C	No	None	--	Continued	-- --
46	69	F 55	Chronic hepatitis	Bowel resection (infarction)	None	Yes (8 mos. preoperatively)	Hypotension	Vasopressors	--	Shock 5
47	69	F 60	Jaundice	Exploratory laparotomy (ca of pancreas)	C	No	Hypotension	Vasopressors	Continued	Shock 4
48	69	M 50	Alcoholism	(1) debridement and skin graft	? C or N	Yes	None	Antibiotics	(42)	(42)
				(2) Same	H	No	None	--	(29)	(29)
				(3) Same	? C or N	No	None	--	10	? Shock 10
49	74	F 34	None	Cholecystectomy, choledochotomy	H (180)	No	None	Chloramphenicol, neomycin steroids	9	Hepatic failure 24
50	74	F 9	None	(1) Dressing, for burns	V, E	Yes	None	Penicillin	(44)	(44)
				(2) Same (7 days)	V, E	Yes	None	--	(35)	(35)
				(3) Same (16 days)	V, E	Yes	None	--	26	G.I. bleeding; ? hepatic failure 8
51	73	M 5 wks.	None	Pyloromyotomy	H (30)	Yes	None	Terramycin, steroid, levulose	5	Hepatic failure 8
52	3	F 39	None	(1) Vein ligation	H	No	None	--	--	(72)
				(2) Same	H	No	None	--	21	Hepatic failure 30
53	63	M 44	None	Herniorrhaphy	H (120)	No	None	--	8	Hepatic failure 12
54	63	M 69	Jaundice	(1) Excision salivary cyst	H	No	None	--	--	
				(2) Cholecystectomy	H (330)	No	None	--	Progressive	Hepatic failure 36
55	63	F 47	None	(1) Nephrectomy	H (120)	No	None	--	--	(35)
				(2) Pneumonectomy	H (240)	Yes	None	--	3	Hepatic failure 16
56	63	F 41	None	(1) Glossectomy	H (105)	No	None	--	--	(55)
				(2) Radical neck dissection	H (180)	Yes	None	--	4	Hepatic failure 17
57	63	F 42	None	(1) Cervical node biopsy	Non-H	No	None	--	--	
				(2) Thyroidectomy, radical neck dissection	H (240)	No	None	--	10	Staphylococcal septicemia 30
58	85	F 56	None	(1) Radium implantation	H	No	None	--	--	(33)
				(2) Same	H	No	None	--	--	(26)
				(3) Radical hysterectomy	H	No	None	--	3	Hepatic failure 5
59	40	F 60	Cirrhosis	Liver biopsy	H	No	Hypotension	Corticoids, vasopressors	3	Hepatic failure ?

Table 3 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
60	40	F 45	History of jaundice	(1) Hysterectomy	H	No	--	--	--	
				(2) Cholecystectomy	H	No	Hypotension	Corticoids, vasopressors	14	Hepatic failure ?
61	40	F 23	None	D & C, colpotomy	H	No	--	--	7	Hepatic failure ?
62	33	M 57	None	Small bowel resection	C (150)	--	Hypotension before operation	Norepinephrine infusion	2	Hepatic failure ?
63	33	F 87	None	Nailing of hip fracture	N	--	--	--	No jaundice	? 12
64	33	F 35	--	Mitral valve prosthesis	N (420)	Yes	--	--	3	Myocardial infarction 27
65	33	F 41	None	Hysterectomy	C (120)	Yes	Shock	Norepinephrine	10	Uremia 21
66	33	M 74	None	Cholecystectomy, drainage of abscess	R	--	--	--	--	Bronchopneumonia, hepatic necrosis ?
67	33	F 54	Metastatic tumor of liver	Exploratory laparotomy, resection of liver (rt. lobe)	C (555)	--	--	--	2	? Hepatic failure 12
68	72	M 59	None	Gastrectomy	H (265)	Yes	None	--	1	G.I. bleeding ?
69	72	M 54	None	? Resection of urinary bladder	H (200)	Yes	Uremia	--	1	Uremia ?
70	72	F 63	None	Gastrectomy, splenectomy, pancreatectomy	H (210)	Yes	Peritonitis, portal venous thrombosis	--	2	Peritonitis ?
71	72	M 59	None	Hemicolectomy	H (215)	Yes	Peritonitis	--	1	Peritonitis ?
72	72	M 70	None	Colostomy	H (135)	Yes	Uremia, peritonitis	--	1	Uremia ?
73	72	M 51	None	Gastrectomy	H (250)	Yes	--	--	2	Pulmonary embolus ?
74	29	-- 74	None	esophagoscopy	H (25)	No	Mediastinitis	--	1	? ?
75	29	-- 65	Cirrhosis	Prosthesis, hip	E (230)	Yes	--	--	? 8	? ?
76	29	-- 60	None	Iliofemoral endarterectomy	E, N, R (305)	No	--	--	2	? ?
77	29	F 47	None	(1) Cystoscopy, D & C, cervical biopsy	C (30)	No	--	--	--	
				(2) Pelvic exenteration	C (3080)	?	Hypotension, staphylococcal respiratory infection, enterocolitis	Succinylsulfathiazole, sulfisoxazole	? 8	? ?
78	29	-- 75	None	Gastrectomy	E (250)	--	Hypotension, subhepatic abscess	--	? 3	? ?
79	29	-- 43	None	Iliofemoral embolectomy	C (205)	--	Septicemia	--	4	Septicemia ?
80	29	-- 78	None	Colectomy	C (330)	--	Pneumonia	Chlorpromazine, phthalylsulfathiazole	4	? ?
81	29	-- 81	None	(1) Abdominal perineal resection and prostatectomy	E (300)	--	Hypotension	Phthalylsulfathiazole		
				(2) Gastrectomy	C (240)	--	--	--	4	? ?

Table 3 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Cause and day of death after operation
82	79	M 46	None	(1) & (2) Excision tumor of cheek	H	No	None	--		
				(3) Same	H	No	None	--	7	
				(4) Same	H	No	None	Prednisone	2	
				(5) Carotid catheterization	H	No	Vomiting	Methotrexate	1	
				(6) Radical neck dissection	N, E	No	None	--		
				(7) Wound closure	N, E	No	G.I. hemorrhage, shock (31 days postoperatively)	--	2	G.I. hemorrhage 34
83	27	M 21	None	(1) Craniotomy	H (300)	--	None	Isoniazid		(13)
				(2) Craniotomy	H (150)	--	None	Isoniazid	No jaundice	Intraventricular bleeding 3
84	58	F 20	None	Cholecystectomy	H (240)	No	None	Acetaminophen, trimethobenzamide, chlorpromazine	9	Hepatic failure 15
85	52	F 23	? None	Craniotomy, posterior fossa	H (300)	Yes	Postoperative respiratory distress	--	No jaundice	Respiratory failure 6?
86	52	F 55	? None	(1) Craniotomy	H (330)	Yes	Brain edema	--	1	(2) (2)
				(2) Craniotomy	?	--		--		Sudden death 1
87	52	F 66	? None	Craniotomy, posterior fossa	H (270)	Yes		--	1	Bronchopneumonia 2
88	52	M 61	? None	Gastrectomy	H (90)	Yes	Preoperative hemorrhage and shock	--	1	Hepatic failure 8
89	52	M 33	? None	Craniotomy	H (240)	Yes	Acute circulatory failure (5 days postoperatively)	--	No jaundice	Circulatory failure 5

TABLE 4.--HEPATIC DAMAGE AFTER ANESTHESIA AND OPERATION--FATAL CASES IN THE LITERATURE (1958-1966), LABORATORY AND NECROPSY FINDINGS*

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
1	44.8										Chronic passive congestion, central lobular necrosis of liver	Changes in liver could have resulted from heart failure
2										Clotting time, 30 min.	Massive hepatic necrosis, pancreatic necrosis	Course and hepatic changes similar to delayed chloroform poisoning
3	3									Urea nitrogen 63 mg %	Acute degenerative hepatitis, renal tubular necrosis	Implicating halothane
4										Bilirubinuria	Massive hepatic necrosis, pancreatic and renal necrosis	Circumstantial evidence was provocative but no proof of halothane poisoning
	11.9	6.7	14.3 (B)	244				10%				
5	23.2	12.2	7.7 (?)	27,000	14,000		8 units				Massive centrilobular hepatic necrosis, cholemic nephrosis	Not possible to determine etiology of liver necrosis, viral or drug induced
6	12.6	4.7		520		3+	5 units	15%			Massive hepatic necrosis	Drug or serum hepatitis
7	81	51	5.8 (B)	180		3+		12%			Centrilobular hepatic necrosis	Hepatic necrosis probably due to drug sensitivity or septicemia
8											Massive centrilobular hepatic necrosis, marked fatty metamorphosis	Hepatic damage similar to that in chloroform poisoning
9											Diffuse hepatic and renal necrosis	Possibility that halothane and chloroform caused toxic effects in a patient with preexisting hepatic disease
10	5.6	1.4							2.5		--	Cause of hepatic necrosis unexplained by operation
11											Acute hepatic necrosis	Cause of hepatic necrosis unexplained by operation
	6.1	1.9	35.6 (KA)	111.5 mm/hr/1					2.75			
12	6.8	1.6									? Atypical myelocytic leukemia	Cause of hepatic deterioration not explained by operation
13	19	9.4	5.9 (KA)	1100				<10%			Acute yellow atrophy	Strong implication that halothane induced hepatic necrosis
14	52		26 (KA)	330		4+	Neg	14		BSP retention, 77%	Massive central and midzonal coagulation necrosis, cholestasis	Strong implication that halothane induced hepatic necrosis
15											Early postnecrotic cirrhosis, wide areas of recent necrosis and regeneration, cholestasis	Strong implication that halothane induced hepatic necrosis
16								<10%			Central and midzonal hyaline hepatic necrosis, bile stasis, renal tubular necrosis	Strongly suggest that halothane may be responsible

*KA, King-Armstrong units; B, Bodansky units; S, Shinowara units; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CF, cephalin flocculation; TT, thymol turbidity; LDH, lactic dehydrogenase; and ICD, isocitric dehydrogenase.

Table 4 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
17										BUN, 96 mg %	Massive hepatic necrosis, renal tubular necrosis, coronary occlusion	Strongly suggest that halothane may be responsible
18											Massive hepatic necrosis, cholestasis, renal tubular necrosis, focal pancreatitis	Implicating halothane as the responsible agent
	29.5		17 (KA)	720	600	2+	+	44 sec				
19	13.2		26 (B)	190		4+	Neg	46%			Centrilobular hepatic necrosis, cholestasis	Strong likelihood that halothane caused jaundice and death
20	36	25	20 (B)	1260						NPN 209 mg %	Massive hepatic necrosis, mild cholestasis, nephrosis	Strong likelihood that halothane caused jaundice and death
21	21.3	7.9	18 (?)	>800	>800		3 units	51 sec	3.6	Zinc sulfate 3 units flocculation	Total necrosis of all liver cells	Hard to prove causal relationship between halothane and hepatic damage
22											Subacute hepatic necrosis, G.I. hemorrhage	Implying causal relationship between halothane and hepatic necrosis
	12			>1000					3.3			
	19.5											
23	13			>150							Acute yellow atrophy, biliary tract normal	"Conjectures regarding causal relationship are valueless."
24										BUN, 142 mg %	Extensive periportal degeneration of liver	"Typical toxic degenerative hepatitis."
25	11.4			35	100						Widespread centrilobular focal necrosis of liver, early postnecrotic cirrhosis	Implicating halothane and radiotherapy
26											Massive hepatic necrosis	Antibiotics and viral hepatitis are possible causes of hepatic necrosis
	9.4	4.3	11 (?)	1250		+	3+	25 sec				
27											Massive hepatic necrosis, no cellular infiltration or proliferation	--
	24.8	13.4		220	540							
28	25.6										Focal areas of centrilobular necrosis of liver	Suggest that prolonged shock and sepsis were responsible for hepatic necrosis
29												Evidence highly suggestive of toxic hepatitis
	13.6		6.8 (B)	650		4+	2.6 units		2.9			
30			39 (KA)	54	34		2+				Liver pale, fatty and friable, suppurative pyelonephritis, pulmonary infarction	--

Table 4 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
31											Acute hepatic necrosis, septic spleen, bronchopneumonia	--
	9.2		44 (KA)				2			Zinc sulfate turbidity, 3 units		
32											Massive hepatic necrosis, no inflammatory infiltration	"A clear cut case of hepatic necrosis caused by halothane."
	1.4											
	14.4		5.6 (?)	1940	2400	Neg	Neg	<10%	2.5	BUN 26 mg%		
33											Advanced hepatic necrosis, minimal mixed cellular infiltration, renal tubular degeneration	"Possible halothane induced hepatitis."
	18.0		20 (KA)	1200	860		3 units			Zinc turbidity 4 units		
34											Hepatic necrosis, renal candidiasis	Toxic hepatic necrosis could not be ruled out
35	6.0			"1.8"							Subacute hepatitis with fatty degeneration	"Cyclopropane hepatitis"
36											Interstitial subacute hepatitis	"Cyclopropane hepatitis."
37											Advanced Laennec's cirrhosis, no necrosis or fatty change, G.I. hemorrhage	"Precipitating cause of fatal liver failure was not known."
			28 (KA)					23 sec				
38	23.2		26 (KA)	1800	748	4+	3+	10%			Central and midzonal coagulation necrosis of liver, cholestatis, renal tubular necrosis	Halothane may have acted as a hepatotoxin
39	3.4		3 (B)	1260		Neg	Neg	10%			Central and Midzonal coagulation necrosis of liver, renal tubular necrosis, pancreatitis	Halothane may have acted as a hepatotoxin
40				58							Massive hepatic necrosis, renal tubular necrosis	Halothane may have acted as a hepatotoxin
	10		20 (KA)	35		Neg	Neg					
41											Massive hepatic necrosis, renal tubular necrosis	Halothane may have acted as a hepatotoxin
	22		17 (B)	374	406	4+	Neg	11%				
42											Liver biopsy after 3rd and 4th operations: focal hepatic necrosis, mixed cellular infiltration; autopsy: parenchymatous degeneration of liver, dilated sinusoids	Causal relationship between halothane and hepatic damage is possible
	20		24.8 (KA)	41.9 mm/hr/1	17.6 mm/hr/1		0.2					
	14.5		35.1 (KA)	7.4 mm/hr/1	7.1 mm/hr/1		0.27			BSP retention (45 min), 36%		
43	24.0		3.8 (B)			4+		15 sec			Massive hepatic necrosis, focal periportal mixed cellular infiltration	Probably viral hepatitis, questionably drug toxicity

Table 4 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
44	10.0		6.4 (B)					23 sec			Massive hepatic necrosis, moderate periportal fibrosis	Probably viral hepatitis
45	30.0		12.3 (B)			4+		16 sec			Massive hepatic necrosis, moderate mononuclear infiltration	Etiology unknown
46			4.2 (B)			3+		27 sec			Cirrhosis of liver, massive parenchymal necrosis	Hepatic necrosis due to prolonged shock and vasopressor therapy, chronic hepatic disease
47	38		11.8 (B)	155		2+		45 sec			Massive centrilobular hepatic necrosis	Prolonged shock and vasopressor therapy
48	3.9		4.5 (B)					16 sec			Massive hepatic necrosis, lymphocytic infiltration with broad bands of connective tissue	? Viral hepatitis, ? halothane hepatitis
49	31	7.5		2150				52 sec			Massive central and midzonal hepatic necrosis, renal tubular degeneration	"Toxic hepatic necrosis."
50											Massive hepatic necrosis, minimal inflammation; renal tubular necrosis	"Toxic hepatic necrosis and nephritis."
				2150				43 sec		ICD 3280 units		
51	30.9	21.8		590							Acute hepatic dystrophy, cholemic nephrosis	Suspicious of causal relationship between halothane and necrosis but no proof
52											Massive hepatic necrosis, pulmonary edema	Cause of hepatic necrosis not indicated by histology
	26.	19.2	23 (KA)	430			2 units			BUN, 30 mg %		
53	5			702	1872			Prolonged			Massive hepatic necrosis, minimal cellular infiltration	Suggest causal relationship between halothane and hepatic necrosis
54											Moderate centrilobular hepatic necrosis, marked cholestasis	Suggest causal relationship between halothane and hepatic necrosis
	28			110				Prolonged				
55											Massive centrilobular hepatic necrosis, cholestasis, active regenerative process	Suggest causal relationship between halothane and hepatic necrosis
	37			1230	2200							
56											Massive centrilobular hepatic necrosis	Suggest causal relationship between halothane and hepatic necrosis
	22			2320				Prolonged				
57												Suggest causal relationship between halothane and hepatic necrosis, liver status improved before onset of septicemia
	34			1400								
58											Massive hepatic necrosis	"Inexplicable by other causes."
	9.4		26 (KA)	1880	11500							

Table 4 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
59			10 (KA)					29%	3.3	Icteric index, 63	Extensive necrosis of hepatic tumor cells, atrophy of central cords	Implicating halothane
60	10.6		15 (KA)	700								Implicating halothane
	56		14 (KA)	1005				< 5%				
61	3.7			2175				12%	3.2		Extensive centrilobular hepatic necrosis	Implicating halothane
62											Acute diffuse hepatitis, lower nephron nephrosis	Specific etiologic factor not stated
63											Early postnecrotic scarring	Specific etiologic factor not stated
64											Focal hepatic necrosis and fatty infiltration	Specific etiologic factor not stated
65											Massy fatty infiltration of liver, lower nephron nephrosis	Specific etiologic factor not stated
66											Massive subscapular hepatic necrosis, pancreatic fistula	Specific etiologic factor not stated
67											Necrosis of liver, left lobe; severe fatty infiltration, splenic infarcts	Specific etiologic factor not stated
68	20.8		6.8 (B)	83	29						Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
69	13.6		10.4 (B)	114	30						Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
70	27.6		18.1 (B)	33	20						Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
71	17.3		4.3 (B)	84	23						Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
72	11.5		2.4 (B)								Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
73	17.1		3.1 (B)								Intrahepatic cholestasis	Benign syndrome resulting from operation, not related to so-called halothane jaundice
74	9.8		7.7	550					2.4		Moderate acute congestion of liver	No evidence to prove that halothane is or is not hepatotoxic
75	46.1		4.7 (B)			4+			2.2		Laennec's cirrhosis with marked necrosis and inflammation	No evidence to prove that halothane is or is not hepatotoxic
76	33.9		11 (B)		141	4+	4+		1.7		Slight fatty change and congestion of liver	No evidence to prove that halothane is or is not hepatotoxic

Table 4 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g %	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
77											Severe fatty change	No evidence to prove that halothane is or is not hepatotoxic
	0.8		8.1 (B)			2+	2+		3.1			
78	2.8		1.8 (B)						3.4		Subhepatic abscess with adjacent necrosis, marked cholestasis	No evidence to prove that halothane is or is not hepatotoxic
79	6.4		12.8 (B)	50					2.6		--	No evidence to prove that halothane is or is not hepatotoxic
80	5.8		6.0 (B)	25					3.6		Nutritional cirrhosis, moderate fatty change	No evidence to prove that halothane is or is not hepatotoxic
81											--	No evidence to prove that halothane is or is not hepatotoxic
	19.0		14.0 (B)	45					2.9			
82											Liver biopsy after 4th operation: cholangitis, fatty change, no necrosis; autopsy: cholangitis, centrilobular hepatic necrosis, fibrosis, fatty change; metastatic tumor in lung and liver, bleeding duodenal ulcer, cholelithiasis	"It appears likely that jaundice after 4th and 5th operations was due to halothane; cholangitis differs from the picture found in most reported cases of post-halothane liver damage."
	4.2	1.6		↑			+					
	14.0		30 (KA)	2360	1060		4 units					
	10.0		30 (KA)	500								
	9.0		~30 (KA)				4 units					
83								Prolonged			Massive hepatic necrosis	Etiology of hepatic necrosis not clear
84	5.5		21 (KA)	7000							Massive hepatic necrosis	No opinion offered
85											Scattered focal hepatic necrosis, fatty change at periphery of lobules; pulmonary infarction, atelectasis, and edema	Death was due to pulmonary changes; fatty change in liver may be toxic in origin
86											Centrilobular focal hepatic necrosis, diffuse fatty change, cholestasis; meningeal hemorrhage, brain edema	Suggesting allergic reaction
87	8.02									Increase in urine urobilinogen	Centrilobular fatty change in liver with cholestasis, severe bronchopneumonia, slight toxic nephrosis	Compatible with toxic hepatosis
88											Diffuse fatty change, cholestasis, and focal necrosis in liver; intra-abdominal hemorrhage	Toxic hepatosis in addition to hemorrhage and shock
89											Diffuse fatty change, cholestasis, and focal necrosis of liver; herniation of brain stem	Death was due to brainstem herniation; toxic hepatosis

TABLE 5.--HEPATIC DAMAGE AFTER ANESTHESIA AND OPERATION--NONFATAL CASES IN THE LITERATURE (1958-1966), CLINICAL HISTORIES

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
1	16	M 46	None	Frontal sinusotomy	H	No	Hypotension during operation	--	? 70	
2	5	M --	None	(1) Prostatectomy	H	--	--	--	Yes, onset not stated	
				(2) Exploratory laparotomy	?	--	--	--		Laparotomy for cause of jaundice; none found
3	5	-- 11	None	Repair, fracture of patella	H	--	--	--	Yes, onset not stated	
4	14	F 51	None	(1) Excision of breast cyst	H (90)	No	None	Bunamiodyl		Fever, RUQ pain, 1 day postoperatively
				(2) Cholecystectomy, choledochotomy	H (210)	No	None	Penicillin	11	
5	54	F 52	None	(1) Arthrodesis, ankle	H	No	None	--	--	
				(2) Joint fusion, foot	H	No	None	--	3	Fever, immediately after operation
				(3) Arthrodesis, toes	H	No	None	--	6	
6	54	F 50	None	(1) Transabdominal polypectomy	C, H	No	Hypotension	Metaraminol	--	
				(2) Exploratomy laparotomy	C	Yes	Hypotension	Metaraminol, tetracycline	22	
				(3) Repair, incisional hernia	H	No	None	--	8	1 year later
7	54	F 62	None	(1) Radical mastectomy	H (540)	Yes	None	--	--	
				(2) Skin graft	H	No	None	--	4	
				(3) Excision, renal cyst	H (100)	No	None	--	5	
8	54	F 60	None	Radical vulvectomy	H (600)	Yes	None	Streptomycin isoniazid, bishydroxycoumarin	No jaundice	RUQ pain, hepatomegaly, x-ray; showed gallstones
9	54	M 59	None	(1) Cystoscopy, proctoscopy	H	No	Perforated ulcer (6 days postoperatively)	--	--	
				(2) Gastrectomy	H	Yes	Thrombophlebitis	--	--	
				(3) Colectomy	H	Yes	--	Bis-hydroxycoumarin	2	
10	54	F 72	None	(1) Breast biopsy	H (180)	No	None	--	--	
				(2) Simple mastectomy	H (125)	No	Chills, fever	--	13	
				(3) Exploratory, laparotomy, cholecystectomy, liver biopsy	C, N (175)	No	--	--	Subsiding	No biliary tract obstruction found
11	54	M 16	None	(1) Aspiration of knee joint	H	No	None	--		
				(2) Arthrotomy knee	H	No	None	--	No jaundice	Splenomegaly, lethargy
12	54	M 34	None	Appendectomy	H	No	None	--	11	Hepatomegaly

*H, halothane; N, nitrous oxide; C, cyclopropane; E, diethyl ether; V, divinyl ether; Ch, chloroform; M, methoxyflurane; Tr, trichloroethylene; and R, regional anesthesia.

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
13	37	M 57	None	(1) Herniorrhaphy	H (120)	No	None	--		
				(2) Phlebectomy	H (165)	No	Pneumonia, staphylococcal	Tetracycline, chloramphenicol, penicillin, diphenhydramine	12	Chills, fever, skin rashes 5 days postoperatively
14	34	F 41	None	(1) D. & C.	H	No	None	Promethazine		
				(2) Spine fusion	H	No	Hypotension	--	7	
15	4	F 42	None	(1) Cervical biopsy	H	No	None	--		
				(2) Radium insertion	H	No	None	--	6	
				(3) Same	H	No	None	--		
				(4) Same	H	No	None	--	Immediate	Hepatomegaly
16	4	F 58	None	(1) Cervical biopsy	H	No	None	--		
				(2) Radium insertion	H	No	None	--		
				(3) Same	H	No	None	--		
				(4) Same	H	No	None	--	Yes, onset not stated	Hepatomegaly
17	4	F 59	None	(1) D. & C., radium insertion	H	No	None	--		
				(2) Radium insertion	H	No	None	--	(21)	
				(3) Hysterectomy	H	Yes	None	--	1	Hepatomegaly
18	25	M 63	--	Cholecystectomy, choledochotomy, appendectomy	E	No	--	--	3	
19	25	M 48	--	Cholecystectomy, repair umbilical hernia	E	No	--	Prochlorperazine	3	
20	25	F 58	--	(1) Cholecystectomy	H	No	Dehiscence	--	5	
				(2) Wound repair	H	No	--	--		
21	25	F 56	--	Cholecystectomy	H	No	--	--	49	
22	19	F 47	--	(1) D. & C.	H	No	--	--	(26)	
				(2) Hysterectomy	H	No	--	--	5	
23	68	F 34	None	(1) Peripheral nerve operation	H	--	--	--		
				(2) Peripheral nerve operation	H	--	--	Steroids	7	
24	49	F 39	Childhood jaundice	(1) Delivery	H	No	None	--		
				(2) Phlebectomy	H	No	None	--	Several days	
25	49	F 23	None	(1) Dilatation of Wharton's duct	H (25)	No	None	--		
				(2) Excision submandibular gland	H	No	None	--	7	
26	82	F 54	None	(1) Carotid arteriogram	H (60)	No	None	Diatrizoate	(19)	
				(2) Craniotomy	H (240)	Yes	None	Penicillin, tetracycline, salicylates	16	Fever
				(3) Carotid arteriogram	H (60)	No	None	Urographin	7	2 years after second operation
				(4) Craniotomy	H (240)	Yes	None	Penicillin, Streptomycin, salicylates	7	

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
27	62	F 57	None	(1) Bunionectomy	H (150)	No	Wound infection	Erythromycin	(33)	
				(2) Amputation, toe	H	No	None	Tetracycline	5	
28	62	M 58	None	Gastrectomy	H (360)	Yes	Transient hypotension during operation	--	4	
29	21	--	--	Gastrectomy	H	Yes	Hypotension during operation	Chlorpromazine, promazine	5	
30	21	--	--	Gastrectomy	H	Yes	Hypotension during operation	--	5	
31	59	M 63	None	Gastroenterostomy	H (75)	No	None	--	3	
32	9	M 57	None	Pyloroplasty	C	Yes	None	Bis-hydroxy-coumarin	5	Lung infarction
33	45	F 51	None	(1) Cholecystectomy	H	--	--	--		
				(2) Thyroidectomy	H	No	None	--	5	Mentally confused
34	13	M 74	None	(1) Cecostomy	H	No	None	--	4	
				(2) Colectomy, liver biopsy	E	No	None	--		
35	64	M 40	--	Gastrectomy, vagotomy	H	Yes	Intraperitoneal hemorrhage	Penicillin, streptomycin, promethazine	5	
36	64	M 32	--	Gastrectomy	H	Yes	--	Chlorpromazine	3	
37	64	M 49	--	Nailing of femur	H	Yes	Hematuria	None	? 12	1 previous operation & 2 subsequent operations all with halothane, uneventful
38	64	M 28	--	Appendectomy	H	No	Ileus	Oxytetracycline, chlorpromazine	? 8	
39	64	M 69	--	Amputation, leg	H	No	None	None	15	
40	64	F 20	--	D. & C.	H	No	--	None	1	
41	64	M 59	--	(1) Nephrectomy	Non-H	Yes	--	None	? 3	
				(2) Wound repair	H	No	--	None	No jaundice	
42	64	M 37	--	Appendectomy	Non-H	No	--	None	3	Cholecystogram: gallstones
43	64	M 65	--	Pneumonectomy	Non-H	Yes	--	Quinidine, streptomycin	6	
44	64	M 38	--	Appendectomy	Non-H	No	--	Streptomycin	5	
45	64	F 14	--	Appendectomy	Non-H	No	--	None	4	
46	64	F 60	--	(1) Gastroenterostomy	Non-H	No	Intestinal obstruction	None	? (21)	
				(2) Reconstruction, gastroenterostomy	Non-H	Yes	None	None	? 1	
47	64	F 76	Hepatomegaly	Colectomy	Non-H	No	? Coronary infarction	Chlorpromazine, neomycin, streptomycin, meprobamate, imipramine	6	

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
48	64	F 29	--	Colectomy	Non-H	Yes	--	Chlorpromazine, neomycin, phthalyl-sulfathiazole	1	
49	39	M 26	--	Herniorrhaphy	H (40)	--	--	--	1 (mild)	
50	39	M 19	--	Appendectomy	H (30)	--	--	--	1 (mild)	
51	39	M 73	--	Colectomy	H (135)	--	--	--	5 (mild)	
52	39	F 14	--	Appendectomy	H (30)	--	--	--	1 (mild)	
53	39	M 46	--	Plastic repair, penis	H (30)	--	--	--	2 (mild)	
54	39	M 27	--	Appendectomy	H (65)	--	--	--	2 (moderate)	
55	39	F 38	--	Gastrectomy, Appendectomy	H (105)	--	--	--	2 (mild)	
56	39	M 24	--	Appendectomy	H (60)	--	--	--	1 (mild)	
57	39	M 27	--	Gastrectomy, appendectomy	H (150)	--	--	--	3 (mild)	
58	39	M 61	--	Gastrectomy, appendectomy	H (195)	--	--	--	3 (moderate)	
59	39	M 18	--	Appendectomy	H (50)	--	--	--	2 (mild)	
60	39	M 31	--	Appendectomy	H (30)	--	--	--	4 (mild)	
61	39	M 29	--	Herniorrhaphy	H (50)	--	--	--	1 (mild)	
62	39	F 19	--	Appendectomy	H (50)	--	--	--	2 (mild)	
63	39	F 32	--	Appendectomy	H (30)	--	--	--	1 (mild)	
64	39	M 59	--	Herniorrhaphy	H (50)	--	--	--	4 (mild)	
65	39	M 23	--	Appendectomy	H (30)	--	--	--	2 (mild)	
66	39	M 48	--	Herniorrhaphy	H (50)	--	--	--	1 (mild)	
67	39	M 54	--	Gastrectomy	H (120)	--	--	--	6 (mild)	
68	39	M 24	--	Appendectomy	H (30)	--	--	--	2 (mild)	
69	39	M 37	--	Appendectomy	H (45)	--	--	--	1 (moderate)	
70	39	M 25	--	Appendectomy	H (75)	--	--	--	4 (mild)	
71	39	M 45	--	Gastrectomy	H (140)	--	--	--	3 (moderate)	
72	39	F 20	--	Appendectomy	H (25)	--	--	--	8 (mild)	
73	39	M 64	--	Gastrectomy, appendectomy	H (105)	--	--	--	4 (moderate)	
74	39	F 42	--	Cholecystectomy	H (90)	--	--	--	1 (moderate)	
75	39	M 59	--	Gastrectomy, appendectomy	H (225)	--	--	--	2 (mild)	

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
76	39	F 15	--	Appendectomy	H (50)	--	--	--	2 (mild)	
77	39	M 60	--	Herniorrhaphy	H (270)	--	--	--	4 (mild)	
78	39	M 53	--	Herniorrhaphy	H (135)	--	--	--	7 (moderate)	
79	39	M 20	--	Appendectomy	H (15)	--	--	--	1 (severe)	
80	39	F 26	--	Appendectomy	H (65)	--	--	--	1 (mild)	
81	39	M 40	--	Herniorrhaphy	H (70)	--	--	--	2 (moderate)	
82	30	F 6	Hepatitis (2 years previously	Ligation patent ductus arteriosus	H (60)	No	None	--	3	
83	10	M 67	Cholestasis	(1) Cystoscopy	H (50)	No	None	Nitrofurantoin, tetracycline	8	
				(2) Prostatectomy	C	No	None	--		
				(3) Cystoscopy	H (45)	No	--	--		
84	10	M 44	None	(1) Carotid arteriogram, craniotomy	H (270)	Yes	None	Chlorpromazine, urografin	6	Transfusion 16 days before operation
				(2) Pneumoencephalogram	H (75)	No	None	--		
85	56	M 5 days	None	(1) Ventriculogram	H (35)	No	None	--		
				(2) Craniotomy	H (75)	Yes	Septicemia	--	3	
86	56	M 3 days	None	(1) Craniotomy	H	Yes	Septicemia	--	14	
				(2) Laparotomy, liver biopsy	H (60)	No	None			
87	56	F 3 days	None	(1) Cystoscopy	H (45)	No	None	--		
				(2) Nephrectomy	H (50)	No	None	--	12	Diarrhea
88	12	M 59	History of jaundice (34 years previously)	(1) Esophagoscopy	H	No	None	--		Hepatomegaly
				(2) Esophagoscopy	H	No	None	--	3	
				(3) Esophagogastrectomy, liver biopsy	N	--	--	--	--	
89	24	M 44	Alcoholism	Hemorrhoidectomy	H (20)	No	None	Promethazine	15	
90	43	M 82	None	(1) Appendectomy	H	No	None	Tetracycline	2	
				(2) Transurethral resection, prostate	H	No	None	--	1	
91	63	F 53	None	Gastrectomy	H (300)	--	None	--	9	
92	63	M 72	None	(1) Bronchoscopy	H (55)	--	--	--	(14)	
				(2) Pneumonectomy	H (330)	--	--	--	7	
93	63	F 55	History of obstructive jaundice	Cholecystectomy, choledochotomy	H (290)	No	None	None	12	Chills, fever
94	63	F 34	None	(1) Cervical node biopsy	H (60)	No	None	--		
				(2) Total thyroidectomy	? H	--	--	--	5	Tetany, chills, fever
95	85	M 77	None	Total parotidectomy	H (225)	No	--	--	3	Hypotensive anesthesia

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
96	85	F 60	None	(1) Radium implantation	H	No	None	--		
				(2) Same	H	No	None	--		
				(3) Same	H	No	None	--		
				(4) Cystoscopy	H	No	None	--		
				(5) Radical hysterectomy	H	No	None	--	4	
97	85	M 48	None	(1) Arteriogram	H	No	None	--		
				(2) Arteriogram	H	No	None	--		
				(3) Craniotomy	H	--	None	--	11	
98	85	M 50	None	(1) Gastrectomy	H	No	RUQ pain (12 days postoperatively)	--		
				(2) Laparotomy	N	No	None	--	(15)	
99	85	M 22	None	(1) Burr hole	H	No	None	--	(18)	
				(2) Burr hole	H	No	None	--	11	
100	40	M 75	Nutritional deficiency	Colectomy	H, C	Yes	None	--	4	
101	40	M 24	Nutritional deficiency	(1) Colectomy	H	Yes	None	--	11	
				(2) Sinus tract excision	H	No	None	--	No jaundice	
102	40	F 22	Nutritional deficiency	Colectomy	N	Yes	None	--	10	
103	40	M 41	None	Vagotomy and pyloroplasty	H	No	Hypotension	Corticoids (preoperatively), vasopressors	5	
104	40	F 41	Previous jaundice	Rhizotomy	H	Yes	None	Corticoids (preoperatively)	1	
105	40	M 75	None	Esophagogastrectomy	H	Yes	None	--	4	
106	40	M 40	Nutritional deficiency	Colectomy	H	Yes	None	--	6	
107	40	F 54	Alcoholism	(1) Repair, retinal detachment	H	No	None	--		
				(2) Same	H	No	None	--	6	
				(3) Same	H	No	None	--	No jaundice	
108	40	M 36	Alcoholism	(1) Repair mesenteric artery	H	No	None	Corticoids	12	
				(2) Laparotomy	C	No	None	--	1	
109	29	-- 52	None	Craniotomy	H (246)	No	--	Chlorpromazine, diphenylhydantoin	No jaundice	
110	29	-- 45	None	Laminectomy	H (110)	No	--	Sulfisoxazole	? No jaundice	
111	29	F 56	None	Radical Mastectomy	H (160)	No	None	--	? 13	
112	29	-- 55	None	(1) Craniotomy	H (250)	Yes	Shock, wound infection	Chlorpromazine, diphenylhydantoin		
				(2) Craniotomy	H (163)	Yes	--	--	? 7	
113	29	-- 64	None	Craniotomy	H (340)	No	--	Diphenylhydantoin	? 1	
114	29	-- 57	None	(1) Incision & drainage, hip	H (64)	Yes	--	--		
				(2) Skin graft, thigh	H (75)	?	--	--	? 10	

Table 5 (Cont'd)

Case	Reference	Sex and age, years	Pre-existing hepatic disease	Operation	Anesthetic agent (duration, min)*	Transfusion	Complications	Drug therapy	Onset of postoperative jaundice, days	Remarks
115	29	-- 20	None	Laminectomy	N (180)	No	--	--	? No jaundice	
116	29	-- 37	None	Gastrectomy	C, E (300)	No	--	--	? 3	
117	29	-- 56	None	Colectomy	C (330)	No	--	Phthalylsulfathiazole	1	
118	72	M 35	None	Lobectomy	H (280)	Yes	--	--	1	
119	72	M 58	None	Esophagectomy	H (290)	Yes	--	Penicillin	1	
120	72	M 21	None	Segmental resection, lung	H (250)	Yes	Hypotension	--	2	
121	72	F 24	None	Exploratory laparotomy	H (185)	Yes	--	--	1	
122	72	M 65	None	Craniotomy	Neuroleptanalgesia (295)	Yes	--	--	2	
123	72	F 42	None	Ileotransversostomy	Neuroleptanalgesia (200)	Yes	--	--	5	
124	89	M 41	None	(1) Dressing, burns	H (90)	Yes	None	Penicillin diazepam polymyxin		All operations within 1 month
				(2) Dressing, burns	H (60)	Yes	None			
				(3) Dressing, burns	H (240)	Yes	None		10	
				(4) Dressing, burns	H (150)	Yes	None		2	

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TABLE 6.--HEPATIC DAMAGE AFTER ANESTHESIA AND OPERATION--NONFATAL CASES IN THE LITERATURE (1958-1966), LABORATORY FINDINGS*

Case	Serum bilirubin, mg %		Alkaline phosphatase, units	SGOT	SGPT	CF	TT	Prothrombin time	Albumin, g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
1											Postnecrotic cirrhosis	? Natural progression of pre-existing liver disease
2												--
3												--
4												Strong implication that halothane induced hepatic necrosis
	13.3	7.0	18 (KA)	1160								
5												Implicating halothane as the responsible agent
	33.5		38 (KA)	146		2+	Neg					
	1.2		33 (KA)	597	880	Neg	Neg					
6												Implicating halothane as the responsible agent
	5.8		57 (KA)			2+	±					
	4.2		54 (KA)	1000		Neg	Neg	16 sec				
7												Implicating halothane as the responsible agent
	4.0		55 (KA)	59		±	Neg	20 sec				
			18 (KA)	340	340							
8	0.8		14 (KA)	480	380	Neg	±		2.3			Implicating halothane as the responsible agent
9												Implicating halothane as the responsible agent
	20.8		42 (KA)	800	1500	±	+	67 sec				
10											Extensive area of hepatic necrosis, most prominent in central zone; gall bladder normal	Implicating halothane as the responsible agent
	18.0		45 (KA)	2800		Neg	Neg	21 sec				
11												Implicating halothane as the responsible agent
	1.0		34 (KA)	540		Neg	Neg	19 sec				
12	8.2		33 (KA)	1730	1270	3+	3+	15 sec				Implicating halothane as the responsible agent
13	4.0	1.7	17 (S)	260	470	4+	14.7 units	80%	2.7	BSP retention (45 min), 69%	Considerable necrosis, collapse of parenchyma, extensive inflammation, fatty infiltration	--

*KA, King-Armstrong units; B, Bodansky units; S, Shinowara units; SGOT, serum glutamic oxaloacetic transaminase, SGPT, serum glutamic pyruvic transaminase; CF, cephalin flocculation; TT, thymol turbidity; LDH, lactic dehydrogenase; and ICD, isocitric dehydrogenase.

Table 6 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phospha-tase, units	SGOT	SGPT	CF	TT	Pro-throm-bin time	Albumin g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
14												? Viral hepatitis
	5.9			450	1000							
15												Wondering if combination of halothane and radium therapy is responsible for hepatic damage
16												Wondering if combination of halothane and radium therapy is responsible for hepatic damage
17												Wondering if combination of halothane and radium therapy is responsible for hepatic damage
	21				310							
18	4.1	0.9										--
19	7.6	1.6										--
20	3.5	1.5										--
21	1.9	0.3	17 (KA)			4+	4		3.7			Probably viral hepatitis
22												--
	3	2.4	20.8 (?)	560			1		4.0	Zinc turbidity, 4 units		
23										"Abnormal liver function tests"		--
24											Mild healing focal hepatic necrosis	Hepatic lesions compatible with damage by exogenous agent
	5.8		48.5 (KA)	3600		4+						
25											Focal centrilobular hepatic necrosis, not significantly different from changes in viral hepatitis	--
	2.2		8.5 (KA)	1120		3+						
26											Inflammatory changes indistinguishable from those seen in viral hepatitis of moderate severity	Hepatitis was probably secondary to halothane
				↑								
			↑	↑								
27												May be coincidental but there does seem to be some evidence of possible halothane hepatotoxicity
	19.0	9.0	29 (?)	1700		+	2+	100 sec				
28	3.3	1.4	26 (?)	108		Neg	Neg	93 sec				Possible causes include prolonged operation hemolysis, viral infection, and antibiotics

Table 6 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phospha-tase, units	SGOT	SGPT	CF	TT	Pro-throm-bin time	Albumin, g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
29	5.9		2.5 (?)	100	88						Centrilobular cholestasis, diffuse fatty change	Difficult to judge cause of hepatic damage
30	1.4		10.4 (?)	40	20		Neg				Centrilobular cholestasis, no necrosis, no inflam-mation	Difficult to judge cause of hepatic changes
31	4.0	1.8	9.2 (KA)	72	54	4+	3.5		2.6	Zinc tur-bidity 12.8; LDH, 200	Patchy necrosis, fatty change	Hepatotoxic reaction to halothane
32	8.5		48.2 (KA)	8.9mM/ hr/l	5.2 mM/hr/ l					BSP reten-tion (45 min), 33%		--
33												Severe hepatitis due to halothane
	18		5.1 (?)	240		4+	9.5	26%	3.0			
34	3.6		10 (KA)	40	40	Neg	Neg	86%			Mild centrilobular hepatic necrosis, cholestasis	Halothane may have acted as a hepatotoxin
35	5.9		7.5 (KA)				1			Zinc tur-bidity, 2 units		--
36	6.2		12.0 (KA)				3			Zinc tur-bidity, 3 units		--
37	5.5		37.0 (KA)	1100	700		12.5			Zinc tur-bidity, 18.4 units		--
38	4.3											--
39	2.0		3.0 (KA)				4			Zinc tur-bidity, 12 units		--
40	2.8		21.5 (KA)				1			Zinc tur-bidity, 7 units		--
41	3.1		14.8 (KA)				36					
	1.0		13.8 (KA)				18					
42	2.0		16.0 (KA)				3.5			Zinc tur-bidity, 7.5 units		--
43	1.4		45.0 (KA)				2			Zinc tur-bidity, 5 units		--
44	2.4		5.3 (KA)	19	29							--
45	2.6		29.0 (KA)	85	325		19			Zinc tur-bidity, 19 units		Clinical diagnosis: viral hepatitis
46												--
	5.0		10.4 (KA)				1					
47	10.0		116.0 (KA)	93	67		3			Zinc tur-bidity, 3 units		--
48	13.3			90	82							--
49	1.5			23	19							--
50	0.6			25	38							--
51	1.8											--
52	1.3			76	63							--

Table 6 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phospha-tase, units	SGOT	SGPT	CF	TT	Pro-throm-bin time	Albumin, g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
53	23			101	76							--
54	1.0			23	16							--
55	1.1			8	11							--
56	1.7			75	60							--
57	2.0			703	250							--
58	3.3											--
59	0.4											--
60	2.8			35	38							--
61	1.0											--
62	1.1											--
63	2.2											--
64	1.4			44	28							--
65	1.3											--
66	1.2											--
67	0.8			83	45							--
68	1.8			50	95							--
69	1.8			50	95							--
70	0.4			50	38							--
71	2.5			121	170							--
72	1.0			60	23							--
73	1.2											--
74	2.8			113	234							--
75	1.4											--
76	0.9			48	8							--
77	1.0											--
78	4.8			370	601							--
79	9.2			2174	3629							--
80	1.4			23	15							--
81	6.6			249	556							--
82	5.4	3.3	19 (?)		14 units							Suggested causal relationship between halothane and jaundice
83	1.2		16.9 (KA)	4.9mM/hr/l	49mM/hr/l	Neg						It cannot be excluded that halothane has caused hepatic damage
84	1.8		14.2 (KA)	3.9mM/hr/l	7.6mM/hr/l	6.1 units						It cannot be excluded that halothane has caused hepatic damage
85	13.6	6.6	107.0 (KA)	84		3 units						No definite association between halothane and jaundice can be established, although it cannot be excluded
86	14.4	9.0	17.0 (KA)	87	57	2 units					Intrahepatic cholestasis, no necrosis, early obstructive biliary cirrhosis	No definite association between halothane and jaundice can be established, although it cannot be excluded
87	8.0	5.0										No definite association between halothane and jaundice can be established, although it cannot be excluded

Table 6 (Cont'd)

Case	Serum bilirubin, mg.%		Alkaline phospha-tase, units	SGOT	SGPT	CF	TT	Pro-throm-bin time	Albumin, g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
88	"Normal"		"Normal"	66		Neg	Neg			ICD, 8.6	Recent centrilobular hepatic necrosis with regeneration, cholestasis	Not possible to draw conclusion, but halothane may cause or aggravate liver damage
	4.1		"Normal"	252						ICD, 6.5		
89	20		31.2 (KA)	492	>500	7 units						Possible causes of hepatitis: halothane, promethazine, viral hepatitis, pre-existing liver disease
90	2.0		4.5 (KA)	31								--
	21		15.3 (KA)	>60	>60					Zinc turbidity, 10 units		
91	2.3			1025	1630							Suggest causal relationship between halothane and jaundice
92												Suggest causal relationship between halothane and jaundice
	3.0			590								
93	1.5			710	520						Variable degrees of eosinophilic degeneration of hepatic cells, diffuse inflammation	Viral hepatitis
94												Suggest causal relationship between halothane and jaundice
	6			1420	860							
95	6		↑	210	200	Neg	Neg					--
96												"Time of onset of jaundice too late to incriminate halothane as a direct hepatotoxin."
	3.3											
97												"Etiology: halothane or viral hepatitis."
	3.3		Normal			Neg	Neg					
98												"Probably viral hepatitis."
				2000				30%				
99												"Likely viral hepatitis."
	9.4			3980	2130	+	+					
100	4.4							48%				Implicated halothane
101	4.4		5 (KA)	135				65%				Implicated halothane
102	6.7			65					2.7			Implicated halothane
103	3.4		5 (KA)	89				77%				Implicated halothane
104	6.3			40				85%				Implicated halothane
105	3.9		4 (KA)	48								Implicated halothane
106	10.5		10 (KA)	460					2.6			Implicated halothane
107												Implicated halothane
	16.5		27 (KA)	2260				48%				
108	5.1		26 (KA)	4300				5%	2.8			Implicated halothane
109	1.5		10.3 (B)			Neg			4.0	BSP retention (45 min), 24%		Recognition of etiologic factors is conjectural
110	0.5		14.6 (B)	185		Neg				BSP retention (45 min), 23%		Recognition of etiologic factors is conjectural
111	13.2		9.0 (B)	375		3+						Recognition of etiologic factors is conjectural
112												Recognition of etiologic factors is conjectural
	4.0		7.4 (B)	125		4+			2.7			

Table 6 (Cont'd)

Case	Serum bilirubin, mg %		Alkaline phospha-tase, units	SGOT	SGPT	CF	TT	Pro-throm-bin time	Albumin, g%	Other laboratory findings	Pathologic findings	Author's remarks or conclusions
	Total	Direct										
113	5.3		8.6 (B)	73		+						Recognition of etiologic factors is conjectural
114												Recognition of etiologic factors is conjectural
	2.9		13.0 (B)	220		3+				BSP retention (45 min), 38%		
115	1.4		13.7 (B)	180		2+			4.7	BSP retention (45 min), 5%		Recognition of etiologic factors is conjectural
116	3.8		20.6 (B)	630		4+			3.8	BSP retention (45 min), 31%		Recognition of etiologic factors is conjectural
117	30.0		17.3 (B)	20		+			3.3	BSP retention (45 min), 17%		Recognition of etiologic factors is conjectural
118	11.0		6.8 (B)	83	29						Cholestasis, steatosis	"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
119	10.8		18.5 (B)	78	40						Cholestasis	"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
120	9.2		16.5 (B)								Cholestasis	"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
121	10.8		13 (B)	57	16						Cholestasis	"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
122	5.7		3.6 (B)	30	25						Cholestasis	"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
123	5.4		4.2 (B)	28	27							"Jaundice is believed to be the result of transient hepatic insufficiency from operation."
124												"Allergic hepatic damage was probably caused by halothane."
			6.1mM/hr/l	30mM/hr/l					2.2	Icterus index, 40 units		
			7.7mM/hr/l	30mM/hr/l			3.5 units	16%	2.5	Icterus index, 130 units		

PART II. DESIGN OF THE STUDY

CHAPTER II-1. APPROACHES TO THE STUDY: A RANDOMIZED TRIAL OR A STUDY OF PAST DATA

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The choice of an experimental design for the National Halothane Study lay between a randomized clinical trial and a population study of past data. This chapter discusses the merits and shortcomings of each, relative to availability and quality of data, simplicity of data collection, cooperation of collaborators, time, manpower costs, and simplicity of procedure.

RANDOMIZED CLINICAL TRIAL

The principle of randomization automatically tends to balance the treatment groups on all factors, such as age of patient and operative risk, whether the factors are known or unknown. This ensures a valid experiment and provides a sound probability basis for scientific inference. Randomization is thus a powerful technique and should be used when it is feasible. But inferences can be correct without randomization; i.e., studies of past data can provide a basis for inference. Inferences from nonrandomized studies are common, for example, in geology, and indeed in many areas of medicine (as in studies of smoking and health). However, in the absence of randomization, corrections must be made for the influence of extraneous factors; sometimes this is adequate to yield inferences that provide a basis for fruitful research, and the replacement of fancy with fact (even tenuous fact) has advanced many an investigation.

A randomized clinical trial initially appeared to be more suitable than a population study for the National Halothane Study. But the randomized trial is approximated only with considerable art, effort, and expense. In a clinical trial of halothane versus other anesthetic agents, which would be aimed at distinguishing between extremely small risks, the numbers of institutions and patients required would be enormous, and the problems of coordination, cooperation, staffing, and training to ensure adequate randomization of all important factors, sobering. There is also the question of whether undetected discrepancies in randomization would be smaller than the undetected biases remaining in a study of past data after adjustment for relevant factors. And, finally, there is some doubt that the considerable medical resources required would be profitably invested in the detection of what might well be a very small lethal effect.

In addition to such considerations of the feasibility of a randomized clinical trial, it is necessary to weigh the propriety of continuing to use a drug already under suspicion. If the suspicion were strong enough to preclude, on ethical grounds, the use of one of the agents, a study of past data would be the only alternative.

In the usual prospective epidemiologic study, treatments are not assigned to subjects randomly. For example, persons cannot be directed to maintain an assigned serum cholesterol level. When treatments can be and are randomly assigned by the investigator, the investigation becomes an experiment, and the length of the chain of inferences from treatment to outcome is reduced. The inferences themselves are usually more absolute. A nonrandomized prospective study of halothane (i.e., without randomization of halothane to some patients and other anesthetic agents to other patients) was never considered, because it seemed feasible to allocate anesthetic agents randomly to the large proportion of patients for whom there would be no absolute agent of choice. Such a controlled prospective study of halothane would be appropriately called a "randomized clinical trial."

The proposed National Halothane Pilot Study originally was designed as a randomized clinical trial in which patients scheduled for surgery under general anesthesia were to be selected at random for exposure to one of several anesthetic agents. Pediatric, obstetric, and emergency patients were to be excluded. The surgeon or anesthesiologist, however, had the option to exclude such controversial or critical cases as cholecystectomy and open-heart surgery, but only before the designation of an anesthetic agent.

Each hospital was to submit each day's surgery schedule, explaining fully which patients were and were not accepted, and the reasons for their selection. The anesthesiologist was to have no knowledge of the agent to be used until he was to prepare for the induction of anesthesia. Preoperative, intraoperative, and postoperative data were to be recorded.

While attempts were being made to improve the protocol and a few institutions were collecting pilot data, halothane became widely publicized as a possible cause of postoperative massive hepatic necrosis. At that time, at least one participating

institution had decided to use halothane only in a small proportion of special cases, but most collaborators were willing to cooperate in a randomized trial and continued to use halothane after the cancellation of the randomized study and during the course of the retrospective study. Thus, the ethical issue might well not have been an overriding factor in the choice of approach if the clinical trial had been the only way of obtaining data on which to base an inference.

POPULATION STUDY OF PAST DATA

A study of past data takes less time and manpower to set up and conduct than a clinical trial. It was believed that the National Halothane Study could, in 1 year, collect information on a sample of all the general anesthetics administered over a period of 4 or 5 years in 30 to 40 institutions. Moreover, the cost was estimated at about one-third that of a randomized clinical trial.

In designing a cooperative study, it is difficult at times to keep the size within the limits of feasibility. However, the temptation to develop an elaborate, comprehensive protocol is much greater in a clinical trial than in a study of past data. For example, participants in preliminary discussions about the protocol of a prospective study suggested that efforts be made to measure hepatic function in all patients, with a 6-week follow-up of each. Despite the laboratory and logistic problems, there would have been great reluctance to let the opportunities afforded by such a trial go by without extra laboratory study and clinical examination of each patient, which would inevitably have led to more missing data, more unfinished cases, less enthusiasm among the participants, and more difficulties in interpretation of the data - which could have led to failure of the study.

We decided that a study of past data should be carried out primarily because it would permit a smaller workload and a shorter completion schedule, and because imbalances in the data would probably be no more serious than undetectable discrepancies in random sampling. This decision was justified further by the belief that a study of past data would provide information that would be useful in planning a randomized clinical trial if the latter proved essential or desirable. It was also argued that the only indications of the toxicity of halothane were those mentioned in scattered cases in the literature or reported to Subcommittee members in private communications. If a systematic study of past data disclosed similar incidents following surgery with other agents, or if the incidence was so low that it was not considered a public health problem, the previous "evidence" might justifiably be dismissed or relegated to its proper perspective and the matter dropped.

In the study of past data, there are two common methods of investigation: the outcome-retrospective method and the historical population study. In the outcome-retrospective method, groups of cases are selected for study on the basis of their outcome. In studying massive hepatic necrosis after halothane, records of surgical patients who died with hepatic damage within 6 weeks of general anesthesia might be obtained and compared with records of patients who died without hepatic damage or with records of a sample of all postanesthesia patients, including survivors. In this approach, the comparison group may be chosen by matching. The selected groups would be examined for differences with respect to the occurrence of the imputed causal factor. In a historical population study, cases are selected to represent the general population. In this instance, patients would be selected from among those who underwent surgery with general anesthesia. Then the anesthetic groups would be compared with respect to outcome, e.g., death or incidence of hepatic damage.

The outcome-retrospective approach was rejected for several reasons:

(1) Incidence rates cannot be computed from data gathered retrospectively unless the magnitude of the source populations that have experienced several outcomes is known.

(2) The sources of bias pointed out by Berkson (1) can be investigated and taken into consideration only with great uncertainty.

(3) The outcome criterion plays a control role; an adequate choice could not have been made in this Study because the nature of the hepatic damage was not (and still is not) well defined.

A study of past experience with halothane and other agents would ordinarily call for selection of surgical patients who received halothane and other patients who received other agents, with a follow-up of the records to determine the number of deaths and the incidence of massive hepatic necrosis in each group. This method seemed feasible and informative. In each hospital, the patients who received halothane and those who received other agents would be counted. Furthermore, all patients who died in the hospital within 6 weeks of general anesthesia could be listed and separated according to anesthetic agent; the presence or absence of massive hepatic damage could then be determined on the basis of necropsy reports. The hospital chart for each patient who survived surgery would not need to be examined, but a sample of all surgical charts would furnish estimates of the numbers of patients to whom halothane and other agents had been administered, according to age, sex, type of operations, etc. This would constitute a standard population study of past data, except that the numbers of patients at risk in various subgroups would be estimated from samples, rather than directly enumerated. Such sampling has no significant effect in principle, but its impact on statistical techniques of analysis is considerable. In view of the over-all advantages, however, this

approach was selected for the National Halothane Study, and new methods of analysis were developed to handle the statistical problems.

The protocol for the pilot prospective study was still being developed when the retrospective approach was selected. It is appended to this chapter for historical purposes, in the hope that it could be helpful to those considering a clinical trial. Details of the protocol, experimental design, and procedures adopted for the population study of past data are discussed in Chapter II-2.

REFERENCE

1. Berkson, J. Limitations of the application of fourfold table analysis to hospital data. Biometrics Bull. 2:47-53, 1946.

APPENDIX TO CHAPTER II-1

PROTOCOL FOR PILOT PROSPECTIVE STUDY*

The great advances of modern surgery have in considerable measure depended on simultaneous advances in anesthesia. Perhaps the most urgent need in the recent past has been for a potent, safe, and nonexplosive anesthetic. The introduction of halothane (Fluothane) in 1956 seemed to meet that need. This agent was introduced after studies of unprecedented thoroughness in animals and humans. Halothane has now been administered to an estimated 10 million patients and appears to have been associated with an extraordinary record of safety. However, in the first few months of 1963 several deaths caused by hepatic necrosis were reported in patients who had received halothane, and the serious possibility has been raised that the anesthetic may have been responsible for those deaths.

It is not possible to determine whether any of the individual deaths reported were related to the anesthetic. Death may have been caused by coincidental infectious hepatitis or by other new drugs, some of which are also suspected of causing hepatic damage and were received by some of the patients. The number of deaths, and hence the incidence, is small, particularly in comparison with deaths from other causes in surgical patients. However, it appears that additional deaths from hepatic necrosis have occurred recently, and have not been reported in the literature, but only by word of mouth. Other anesthetics, as well as halothane, had been received by some of these patients.

The recent experience points to an urgent need to determine whether halothane damages the liver. That it might has long been suspected because of its chemical similarity to chloroform, which is known to produce fatal hepatic damage. The urgency to examine the safety of halothane is especially great in view of the remarkably favorable qualities associated with its use and in view of its current popularity (it is estimated that half the operations in the United States are performed with halothane).

OBJECTIVES

The proposed research plan is designed to answer the following questions:

(1) Does halothane damage the liver? More precisely, is there an association between the use of halothane and the occasional appearance of postoperative hepatic damage whether fatal or nonfatal?

(2) If so, what is the incidence of postoperative hepatic damage after halothane, and is it greater than the incidence after other commonly used anesthetic agents?

(3) Under what circumstances does halothane damage the liver? Are some patients more susceptible to hepatic damage than others? For example, is the patient undergoing cholecystectomy, with the possibility of some degree of pre-existing hepatic disease, more susceptible to the toxic effects (if any) of halothane? (This question and others like it are of less importance than those in paragraphs 1 and 2, and are less likely to be answered.)

(4) If fatal hepatic necrosis occurs in some patients after exposure to halothane, does halothane possess sufficient advantages to justify accepting the risk to the liver? For example, the fragmentary evidence available from retrospective studies in progress suggests that the incidence of fatal hepatic necrosis after halothane may be around one in 5000 or 10,000. An over-all mortality of approximately one in 1000 has been attributed to general anesthesia by Beecher and Todd, who found, in the same study, a death rate of approximately one in 75 from all causes in surgical patients. It is not unreasonable to expect that the favorable qualities of halothane, if they are as great as has been claimed, would be reflected in a decrease in mortality associated with general anesthesia or in total surgical mortality.

(5) What is the over-all incidence of postoperative hepatic damage? It should be possible by comparison with the control group to separate at least the effect of halothane, and to obtain some information concerning the effects of other factors on postoperative hepatic difficulties.

THE CHOICE OF AN EXPERIMENTAL APPROACH

There are a number of serious problems in designing a clinical trial to answer the foregoing questions. The most difficult is the apparent infrequency of the complication in question. Although retrospective information is scanty, it appears most unlikely that fatal hepatic necrosis occurs more frequently than once in every 5000 cases. Information on the occurrence of nonfatal hepatic failure is, if anything, less satisfactory, but its incidence may be five or 10 times that of fatal hepatic necrosis.

A second serious difficulty, and one that has hampered the collection of dependable case reports from past experience, is the apparently late appearance of the clinical manifestations of hepatic damage. Many patients have been discharged on the 5th or 6th postoperative day, to be readmitted as late as the 12th or 14th postoperative day with jaundice, usually thought to be a manifestation of infectious hepatitis.

*Adapted from working protocol prepared in August 1963; implemented in only one institution.

It would be highly desirable to be able to recognize such patients before their discharge, i.e., in the early postoperative period, and it has been suggested that serum glutamic oxaloacetic transaminase (SGOT) might be measured on approximately the 5th postoperative day, in an attempt to determine hepatic damage that is not yet clinically manifest. Unfortunately, data are not available that allow us to assume that measurement of SGOT will help in this matter. If a drug has a direct toxic effect on the liver, it is highly likely that this would become apparent by the 5th postoperative day, both clinically and by tests of hepatic function. But it is suspected that, if halothane does damage the liver, the damage is not caused in the same manner as that caused by chloroform and carbon tetrachloride (i.e., by a direct toxic effect), but rather results from some other mechanism, such as a sensitivity reaction. If that is so, and if hepatic damage can occur as late as 2 weeks postoperatively, there is no reason to assume that any test on the 5th postoperative day could predict it.

Another major difficulty is the effect of bias on the interpretation of individual case material. It is agreed that the end points should be fatal and nonfatal clinical disease. The diagnosis of hepatic damage and, in fact, the simple observation of lesser degrees of jaundice, is open to considerable subjective interpretation. A patient with a low-grade fever or a moderate increase in white-cell count, observed under indirect lighting in such a way that the color of the sclerae may not be easily determined, is much more likely to be subjected to a battery of hepatic tests and intensive study if he has received halothane than if he has received a drug that is not under suspicion. Even the interpretation of fatal cases is subject to serious bias.

The possibility of answering the questions listed above from an examination of past experience seems unlikely. Examination of published reports alone is of no help, because the finger of suspicion has been raised; hepatic necrosis after halothane can be expected to be reported, whereas hepatic necrosis after agents not under suspicion almost certainly is not being reported.

An examination of the total experience of a single institution over the last 5 years, which has already been attempted, showed that anesthetic agents are used in a highly selective way and one may expect to find that as many as 90 percent of patients who have undergone a particular operation have received halothane. Another difficulty that has been encountered in attempts to derive information from card indexes in hospitals is that hepatic-related deaths are not likely to be adequately coded; e.g., in one large institution, during a period in which 160,000 anesthetics had been given, not a single instance of hepatic necrosis was cross-indexed in the system.

The approach most likely to accomplish the objectives would be a prospective study comparing halothane with nonhalogenated agents, the two treatment groups being carefully randomized. It is anticipated that a large volume of patients will be needed, and, accordingly, a large number of institutions. It is therefore essential that the experimental approach be as simple as possible to permit coordination.

In view of the apparently late appearance of hepatic damage in the suspected cases, careful follow-up will be essential. The recognition of hepatic damage will depend on careful clinical observation in the postoperative period, and in the 2-week follow-up. Furthermore, patients still in the hospital on the 5th postoperative day will undergo an SGOT test and, if SGOT is elevated, detailed studies of hepatic function. The usefulness of the SGOT procedure for this purpose is by no means clear and its evaluation will be an important objective of the pilot study. A urine sample will be taken from all patients to determine the presence or absence of bile on or about the 14th day. If bile is present, blood will be drawn for complete hepatic-function studies and the patient's physician will be informed of the possibility of hepatic damage.

Many of the difficulties of experimental design in a prospective study of the kind contemplated can be related to the fact that (as originally planned) the choice of anesthetic agent would be known to the investigative team and to the physicians caring for the patient. At first glance it would appear impossible to conceal the choice of agent, and not necessary if the evaluation of results could be kept entirely objective. If the screening of patients could be safely entrusted to the SGOT test, as we hoped would be possible, and if the evaluation of hepatic damage could be precisely related to disturbances in hepatic function, the need for a "blind" study might appear minimal.

Even if this idealized approach were possible, as now seems unlikely, one can anticipate many opportunities for serious error in an "open" study. The recognition of the need for a prolonged follow-up and the emphasis on clinical evidence of hepatic damage make it imperative to use the blind approach. The reasons are suggested in the paragraphs that follow.

It is planned that a nurse technician will follow the clinical course of each patient in the hospital and record specific information on the Study charts. Such information will be derived largely from the patient's record, but specific clinical observations will also be made, e.g., she will examine the sclerae for icterus. If she believes the sclerae to be yellow, she will draw blood for appropriate hepatic-function tests, including measurement of bilirubin, and inform the internist member of the Study team of the possibility of hepatic damage. Inasmuch as highly competent physicians, in our experience, have been grossly inaccurate in the detection of lesser degrees of scleral icterus (as documented by serum bilirubin determinations done later in the

same day), it is too much to expect that a nurse can do better. It goes without saying that, if she has any preconception that halothane may damage the liver, her suspicion will be greater if she knows that halothane has been used.

If it were possible (which is doubtful) to define the functions of the nurse technician in such a way that her observations could be unquestionably objective, a more serious difficulty immediately intrudes itself, namely, that the actual care of each patient will be in the hands of physicians entirely separate from the Study team. These physicians will make observations and order laboratory tests as they believe indicated. The patient given halothane would be likely to undergo tests of hepatic function earlier than other patients, and there is no question but that disturbances made evident by hepatic-function tests will influence the clinical evaluation of the postoperative state of the liver. In a retrospective study of the hepatic effect of anesthesia in patients who had undergone surgery for portal hypertension, we encountered precisely this problem: patients who had received one anesthetic agent had multiple hepatic-function tests, whereas those who had received a different agent had few tests. It was clearly shown that this contrast seriously biased the final clinical evaluation.

It is proposed that the follow-up visit, presumably at the patient's home, will include, and depend very heavily on, a urine test for bile. This would appear to be wholly objective. However, 100 percent follow-up will be impossible and the amount of effort made to obtain the urine specimen will most likely vary with the degree of suspicion, i.e., with the anesthetic agent used. Furthermore, subjective bias becomes an even greater problem if there is any effort to evaluate the patient's general condition - fatigue, jaundice, tenderness over the liver, etc.

In the evaluation of deaths, one would at last seem to be on firm ground. The microscopic sections of the liver will be evaluated by a panel of pathologists and specialists in medical aspects of hepatic disease who will know nothing about the clinical course and whose interpretation can be depended on to be completely objective. However, it is clear that clinical events will play a very important role in the evaluation of each death. In any final analysis of mortality, it will be desirable to eliminate patients who died from other obvious causes; the physicians most capable of such evaluations are those directly concerned with the care of the patients. Again, the bias that inevitably accompanies knowledge of the anesthetic technique can negate any efforts to make objective judgments.

A very valuable kind of information that will be particularly important in any attempt to evaluate effects other than those on the liver is the separation of deaths into "patient's disease" "surgical deaths," and "anesthetic deaths," as is common in many teaching departments. If the anesthetic death rate is significantly affected in either group, that can markedly alter our final interpretation of the significance of any anesthetic effects on the liver that may be detected. The separation of deaths into these categories, however, is highly subjective, with a high probability of variation in interpretation. These evaluations must be made by the physicians on the scene, as emphasized by Beecher and Todd, and would clearly be very sensitive to bias.

One might question whether the choice of anesthetic agent can ethically be concealed and whether such concealment might prejudice the care of the patient. This need not be the case if all patients are treated as though they had received halothane, which is not unreasonable, inasmuch as it is agreed that each patient is suitable to receive halothane before he is admitted for the Study.

One might also wonder whether it is even possible to conceal the choice of anesthetic agent. In actual practice today, the surgeon rarely knows which agent is being used, and is usually grateful to be able to turn over everything in this area to the anesthesiologist. To be sure, the recent halothane scare has forced him to be more conscious of which agent is used. If the surgical team is to remain blind to the choice of agent, the surgeon must be willing to accept this condition. His very willingness to participate in the proposed Study implies his agreement as to the importance of the project and its objectives; thus, he is presumably willing to accept any reasonable and necessary provisions. It should be clear, of course, that whenever it becomes essential to identify the anesthetic agent, the code may be broken; but that is not expected to be common.

If an explosive anesthetic agent is to be used in the control group, it will be difficult to conceal the fact that halothane is not being used. To correct for this in institutions where explosive agents will be used in the control group, one might simply suggest that all patients, whether halothane or control, be treated as though an explosive agent were to be used.

On the same subject, there is something to be said for avoiding explosive agents entirely in the control group, in that, particularly with the increased use of electrocoagulation for control of bleeding, the choice is usually between one nonexplosive technique and another, and a comparison between halothane and a technique involving intravenous drugs, particularly in terms of their effects other than those related to the liver, may be more meaningful.

It is clear that, if the identity of the anesthetic agent is to remain unknown, conduction anesthesia cannot be accepted as control technique.

SAMPLING PLAN

It is to be hoped that the results of the Study will be applicable to as wide a group of patients

as possible; by this token, it is preferable to make as few exclusions as possible. If, for example, the Study patients were limited to good-risk young men 20 to 30 years old, and no differences in hepatic effects were found, it would be hard to claim that this result could be expected to apply to all surgical patients.

Special attention has been focused on the possible relationship between biliary tract operations and hepatic necrosis after halothane anesthesia. Thus it might appear to be particularly desirable to know whether this group is especially sensitive to any possible effects of halothane on the liver, but one might also be reluctant to subject such patients to halothane if it is expected that there is an increased risk. One might omit such patients initially, and include cholecystectomies later if no differences were found in other patients. Inclusion from the outset, however, has a very special advantage in that if the incidence of hepatic difficulties after cholecystectomy is greater, we are likely to have an answer earlier than if these patients are excluded initially. There is, in fact, good justification for their inclusion: preliminary conclusions from on-going retrospective studies suggest that hepatic necrosis appears no more frequently after cholecystectomy under halothane than after cholecystectomy under other agents. It is possible that more information on this group of patients can be obtained soon and can help to form the basis for their inclusion in the Study.

It would appear to be appropriate to include cardiac surgery, unless an individual institution considers halothane essential to safe anesthesia for these patients (as is the case in many medical centers). Children of all ages may be included, but blood samples for SGOT tests will be omitted below the age of 10 (possibly 8) years. Evaluation of such children will necessarily be clinical during the early postoperative period, but the 14-day urine test will be included.

Because the emphasis on the SGOT test for screening will be less than originally planned (or, in any event, because its inclusion now is still on a pilot basis for later reconsideration), there appears to be no reason to exclude patients who may be discharged before the 4th or 5th day; of course, such patients should be seen on the 14th day and a urine sample should be taken then.

Obstetric patients and the newborn, as originally planned, will be excluded from the Study.

Emergency procedures are excluded, simply because of the technical problems involved in the collection of preoperative data, the drawing of blood samples, etc.

SPECIFIC PROCEDURES

Each institution will select its subjects from the operating schedule on the following basis:

(1) Emergency patients, obstetric patients, and neonates will be rejected automatically.

(2) The following categories will be subject to local interpretation:
   (a) noncooperating surgeon,
   (b) noncooperating anesthesiologist,
   (c) noncooperating patient,
   (d) jaundiced patient,
   (e) patient undergoing surgery for gall bladder disease, and
   (f) patient who will not tolerate halothane or other inhalation agents.

Every attempt should be made to use patients who will have a hospital stay of 5 days or longer. Therefore, before final selection, patients should be rated as follows: if the stay is to be 5 days or longer, rate as group 1; and if the stay is to be shorter than 5 days or the patient is under 10 years old, rate as group 2. Include group 1 patients in preference to group 2 patients. If there are more in group 1 than one could normally handle, select them alphabetically according to anesthesiologist; if there are too few in group 1, include patients from group 2.

When the anesthesiologist designates a Study patient according to the definitions and restrictions in the protocol, he must code all possible open boxes of the National Halothane Study Form (NHSF) (Fig. 1) before the random selection of the anesthetic agent. Presumably, this would be done during preoperative rounds. Just before the induction of anesthesia, the agent is identified. A decision to exclude a patient must be made before identification of the anesthetic agent.

The procedure for selecting anesthetic agents is as follows. Random numbers will be taken from the Statistical Tables for Biological, Agricultural and Medical Research;* these tables allow for 15,000 serially selected random numbers for assignment of agent. Serially numbered envelopes with cards will be prepared from random numbers designating halothane or non-halothane at a central office and distributed to participants. When the envelopes have been distributed to the participating institutions, the small envelopes should be assembled and a signoff sheet placed at a location convenient for the attending anesthesiologist. He should pick them up just before administration of the anesthetic. It should be stressed that all open boxes on the NHSF are to be coded before the anesthetic selection is made. The number on the selection envelope should agree with the number on the assignment sheet and with the serial number of the NHSF. Forms will have to be stored in a place convenient to the area of preoperative rounds.

A register should be signed, indicating for each serial number the patient's name, the time the card was picked up, and the anesthesiologist's name.

*Fisher, R. A., and F. Yates. Statistical Tables for Biological, Agricultural and Medical Research, p. 126 (5th ed.) London: Oliver & Boyd, Ltd., 1957.

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If, after one has selected the agent card, the case is canceled or the choice is not carried through, a note of explanation should accompany the appropriate NHSF. If a patient is excluded from the Study after the selection of the anesthetic, an after-the-fact deletion form must be completed, including the serial number of the NHSF and assignment packet, the patient's name, the anesthesiologist's name, the institution code, and statements of whether the case was canceled (and, if so, whether the cancellation was related to the anesthetic choice) and whether a new indication became available after assignment.

A copy of each day's operating schedule must be prepared and submitted with the Form One, Part One (see Fig. 1). Each case should be marked "Study," "Excess," or "Excluded." "Excess" refers to patients found suitable for inclusion, but in excess of needs or capacity for that day and therefore omitted. "Excluded" cases should be so indicated and the explanation for each case given. The operating schedule and the completed Part One should be mailed to the central office at the end of each day, with the signoff sheet for that day and other data if necessary (e.g., deletion forms).

After preanesthetic medication and before induction of anesthesia, a blood sample is to be obtained for the determination of SGOT level. This value serves as the preanesthetic control, $SGOT_1$.

The induction of anesthesia is left to the discretion of the anesthesiologist within the definition of the protocol (i.e., halothane as ordinarily used, or other agents as ordinarily used). Among the anesthetic techniques excluded from the Study are: other halogenated agents, regional anesthesia (regional anesthesia in combination with general anesthesia is acceptable), local anesthesia, and hypnosis. At the end of the anesthesia, the remaining open boxes of the form should be completed. This satisfies the anesthesiologist's obligation for completion of the form, because it is planned that a nurse technician, who will not know the identity of the anesthetic, will record postoperative data on a separate form.

The original copy of the anesthetic record should be removed from the chart, because that would identify the anesthetic technique. The carbon copy should not show the anesthetic technique and may remain on the chart. Thus, we maintain a blind approach. The original of the anesthetic record should not reappear on the chart until discharge of the patient from the Study (not necessarily from the hospital).

A blood sample is to be obtained on the 5th* postoperative day for SGOT determination ($SGOT_2$), as well as white-blood-cell and differential counts. If the postoperative SGOT level is higher than 75 units, detailed hepatic-function studies are to be carried out, including serum bilirubin, alkaline phosphatase, thymol turbidity, cephalin flocculation, and punch biopsy of liver if possible (and perhaps prothrombin time). Follow-up study is to be done as indicated.

For patients who have multiple operations, the same random selection is to be used for subsequent procedures. Patients exhibiting hepatic damage after anesthesia will be designated as reactors. In such a patient, the choice of anesthesia for subsequent operations is left to the discretion of the attending anesthesiologist. However, if he thinks that the patient can be reentered into the Study within the bounds of the protocol, this should be done. If one does not include the patient as a randomly selected subject, then the special instruction should be followed. Hepatic function will be studied after each subsequent anesthesia, irrespective of the agent used. (Any patient readmitted to Study for a second or later procedure should undergo preoperative and 5th-day postoperative batteries of hepatic-function tests, as listed in the previous paragraph.)

*May be drawn on the 4th day if the patient is likely to be discharged before the 5th day, or on the 6th day to miss a weekend, or if for some other reason the 5th day is missed.

RECORDING OF DATA

Data available before, during, and after operation:

The following data are to be recorded by the anesthesiologist for subsequent statistical analysis:

(1) Preanesthetic: Name, unit number, date of birth, sex, physical status, number of anesthetic exposures within past year, preoperative diagnosis, significant preoperative complications, drug therapy and duration, alcoholic intake, history of recent blood transfusion, preanesthetic medication, and $SGOT_1$ level; specific statement of jaundice, recent or past; dietary habits, intravenous or oral intake, including specific statement of caloric intake during 36 hr immediately preoperatively; history, including biliary tract disease, pancreatitis, malnutrition, weight loss (specify), obstetric history (specify complications), allergy, drug reaction, dental work, and recent congestive heart failure.

(2) Physical findings: Jaundice, edema, ascites, spider nevi, liver size, splenomegaly, cyanosis, clubbing, pulmonary congestion, venous congestion, fever, and hypertension (specify).

(3) Anesthetic: Primary and secondary anesthetics, other medications, and duration of anesthesia and operation; respiratory, circulatory, and other complications; fluid therapy and blood transfusion; controlled, assisted, or spontaneous respirations; concentration of halothane (if used) and type of vaporizer; halothane freshly opened?; lowest blood pressure (specify); and use of vasopressors.

A specially trained nurse will record the following on Form One, Part Two:

(4) Postanesthetic: Highest temperature, fever, chills, rash, nausea, vomiting, upper abdominal pain, anorexia, hypotension (specify lowest systolic pressure), duration of hypotension, use of vasopressors, and jaundice (if present, specify whether accompanied by pruritus, dark urine, light stools, ascites, edema, stupor, or hemorrhage).

The patient will be instructed on discharge to send to the hospital via special delivery mail a urine sample on the morning of the 14th postoperative day, and will be given a special container and mailing envelope for this purpose. The nurse technician will telephone the patient on the 14th day to remind him to send the sample, and in addition will question the patient regarding those signs and symptoms listed above, as postoperative follow-up. If the urine has not arrived by the following day, a second telephone call will be made to try to obtain it. If this is not successful, a house visit may be necessary.

The internist member of the team will follow patients if: (1) the $SGOT_2$ is above 75 units; (2) hepatic damage is suspected by the nurse technician or by ward surgeons; or (3) urinary bilirubin is elevated on the 14th day. It is imperative that both the nurse technician and the internist remain blind to the anesthetic procedure at all times.

Necropsy data:

If a necropsy is obtained, the pathologist should remain blind to the anesthetic agent. A copy of his pathology report will be sent by the nurse technician, a secretary, or another locally designated person to the Collection Center. In addition, necropsy material will be requested for submission to the Pathology Review Board. It is urged that in all cases, whether or not permission for necropsy is anticipated, a postmortem needle biopsy be obtained immediately after death (the time between death and biopsy should be recorded). A report on the findings of the needle biopsy should be sent to the Collection Center; again, it is hoped, the pathologist will be blind to the anesthetic agent.

Laboratory data:

The clerk will record pertinent laboratory data. All patients will have a preoperative hemoglobin or hematocrit measurement, white-cell and differential counts, and $SGOT_1$ test. All patients will be studied for SGOT and urinary bilirubin on the 5th day, if still in the hospital. All patients will be studied for urinary bilirubin on the 14th day. If the $SGOT_2$ is elevated or if either of the urine bilirubin readings is elevated, a liver profile is in order. If the clinical course of the patient is such that the internist is called to see him, then the results of the laboratory tests should be recorded.

Data on patients undergoing multiple operations:

Any patient reoperated on since the beginning of the Study should be suspect. If the history of previous inclusion can be obtained, it should be noted on Form One, Part One that the patient is a repeat under previous inclusion. He can be categorized as reactor or nonreactor.

"Reactor" (as distinct from "hepatic damage") will have to be defined most specifically, and should probably include elevated $SGOT_2$, clinical jaundice confirmed by serum bilirubin above 2.0 mg percent, and bile in 14-day urine.

A repeat should have a liver profile done on day 1, as well as on day 5, whether he was previously a reactor or not.

For the purpose of this Study, "hepatic damage" will be defined on the basis of elevated $SGOT_2$, clinical jaundice shown by a serum bilirubin above 2.0 mg percent or disturbances in other tests, and bile in the 14-day urine.

HANDLING AND GENERAL ANALYSIS AND INTERPRETATION OF DATA

The statistical evaluation of the data will be based on the correlation between the laboratory findings and the total clinical picture. It is hoped that a cutoff point can be defined after pilot data are collected, so that patients may be divided into specific categories.

In the presence of hepatic damage, other possible etiologic factors, such as history of blood transfusion and therapy with drugs of hepatotoxic potential, may be implicated. In a patient whose $SGOT_1$ is elevated, the significance of hepatic damage, if present, may be most difficult to assess. Such cases will be treated separately in the final analysis, as will patients who are reactors and who have multiple anesthetics, including those who enter the Study more than once.

Handling of forms and data processing

(1) 1st postoperative day - Send via airmail to Collecting Center:
   (a) Form One, Part One, completed,
   (b) complete surgical schedule, with description of exclusions, and
   (c) sign-off sheet and after-the-fact deletion form.
(2) Nonreactor 15th postoperative day - Send Form One, Part Two to Collecting Center via airmail, and retain Part Three.
(3) Reactor, nonfatal - Send Form One, Part Two when discharged from Study by internist.
(4) Reactor, fatal - Send Form One, Parts Two and Three with necropsy report to Collecting Center; send necropsy material to consultants for pathology review (blind).

Center handling of data

(1) Secretary receives daily report from each institution, checks for errors of omission, and sends immediate request for correction on separate sheet.
(2) Registration and logging of reports:
  (a) number from each institution,
  (b) number of errors from each institution, and
  (c) weekly reports to Dr. Forrest.
(3) Entry of diagnosis by international code.*
(4) Card coding and printout to check for errors.
(5) Filing of data cards.
(6) Monthly report from each institution to Dr. Seeley, Dr. Bunker, and Dr. Forrest:
  (a) total number of entries,
  (b) number completed and coded,
  (c) number of errors, and
  (d) suggestions.

Coordinator will make frequent visits to participating institutions for indoctrination, laboratory check, adherence to protocol, adherence to double-blind method, troubleshooting, and discussion of reports.

*International Classification of Diseases. 1955 Revision. Volumes 1 and 2. Geneva: World Health Organization, 1957.

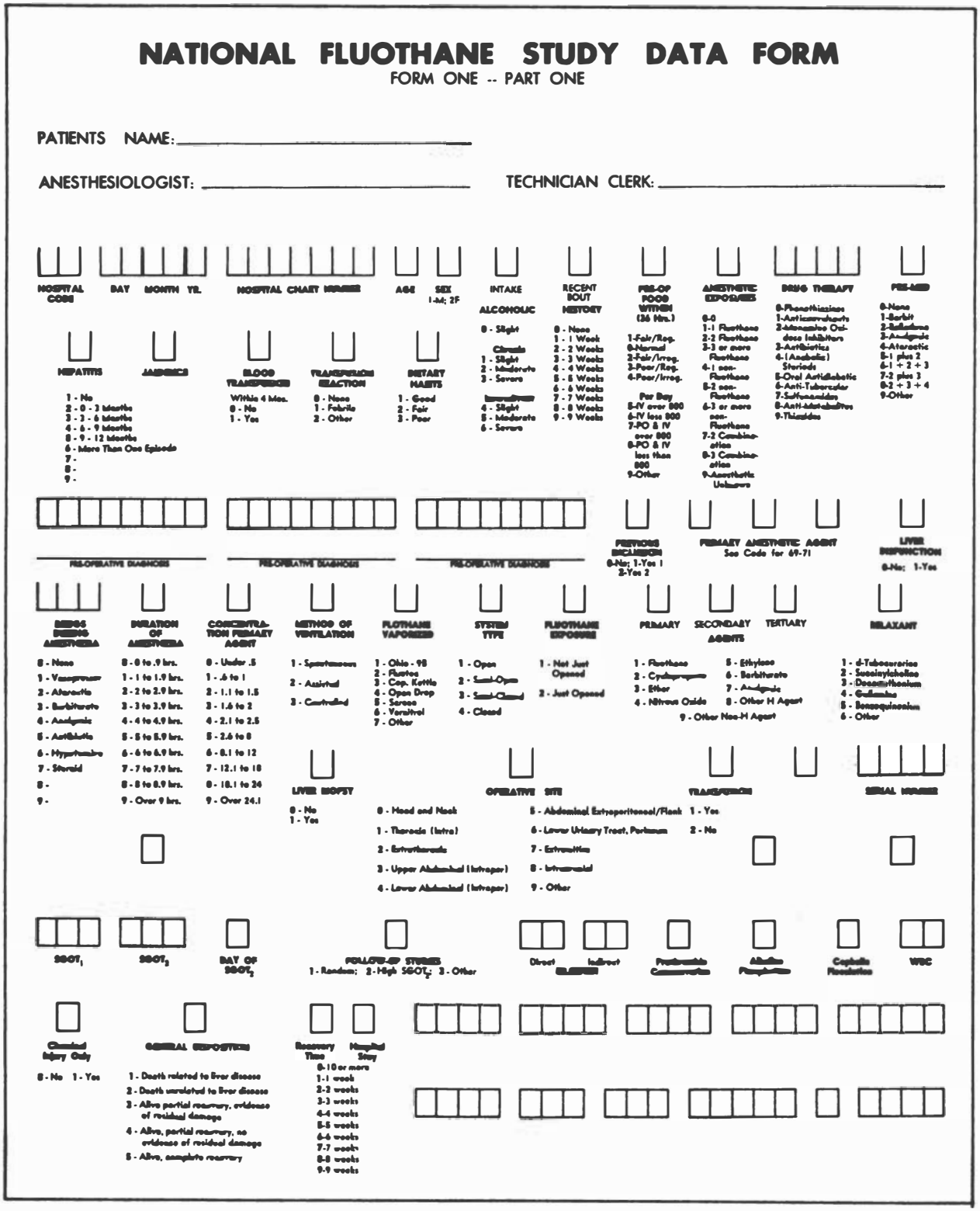

Figure 1.--National Halothane Study Form One. This form consists of three parts, which are virtually identical (the patient's name appears only on Part One). Part Two is designed for ease of punching to Hollerith cards. Part Three is stiffer, for use as a permanent record of the Study.

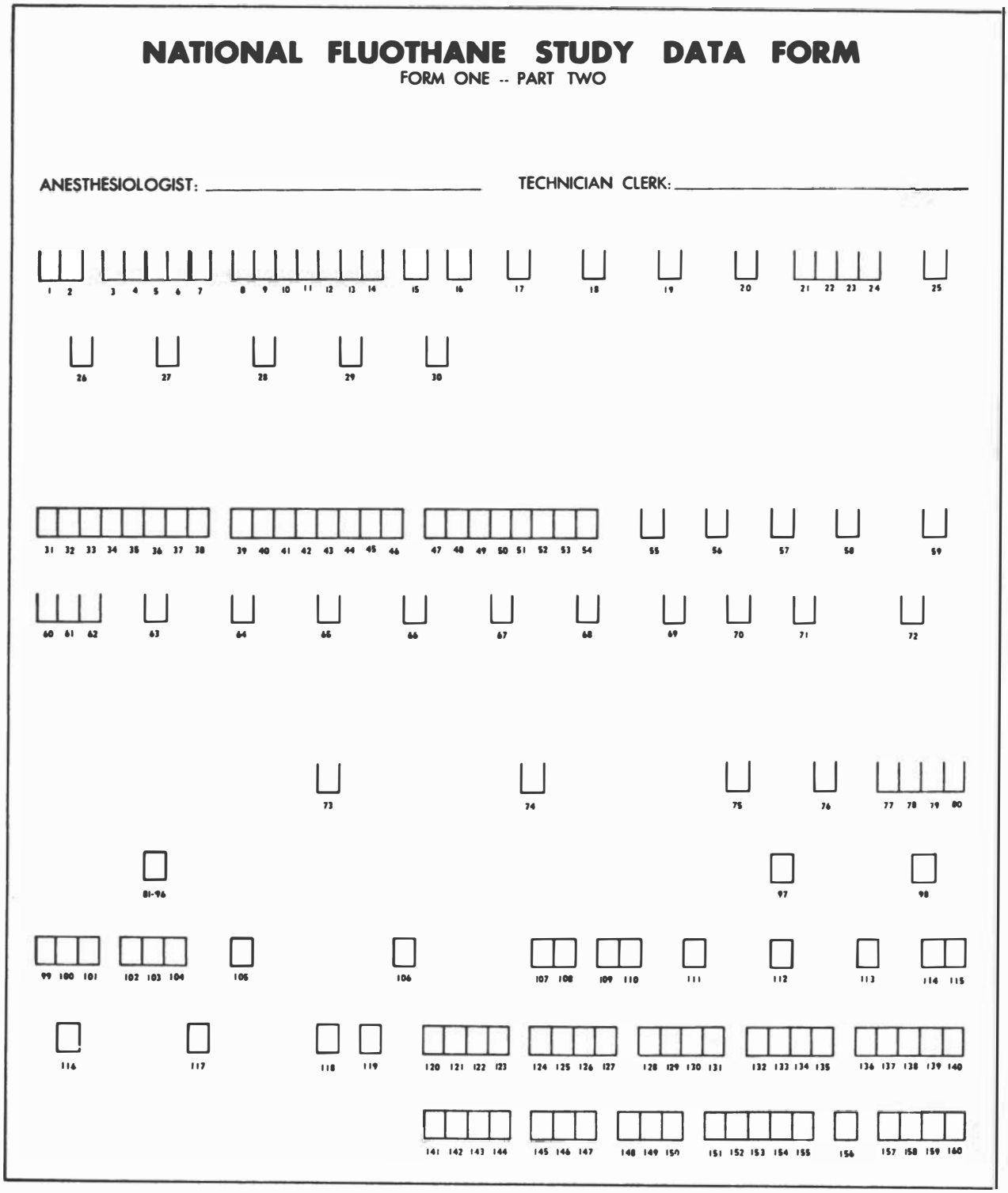

Figure 1 (Cont'd)

NATIONAL FLUOTHANE STUDY DATA FORM

FORM ONE -- PART THREE

ANESTHESIOLOGIST: _____ TECHNICIAN CLERK: _____

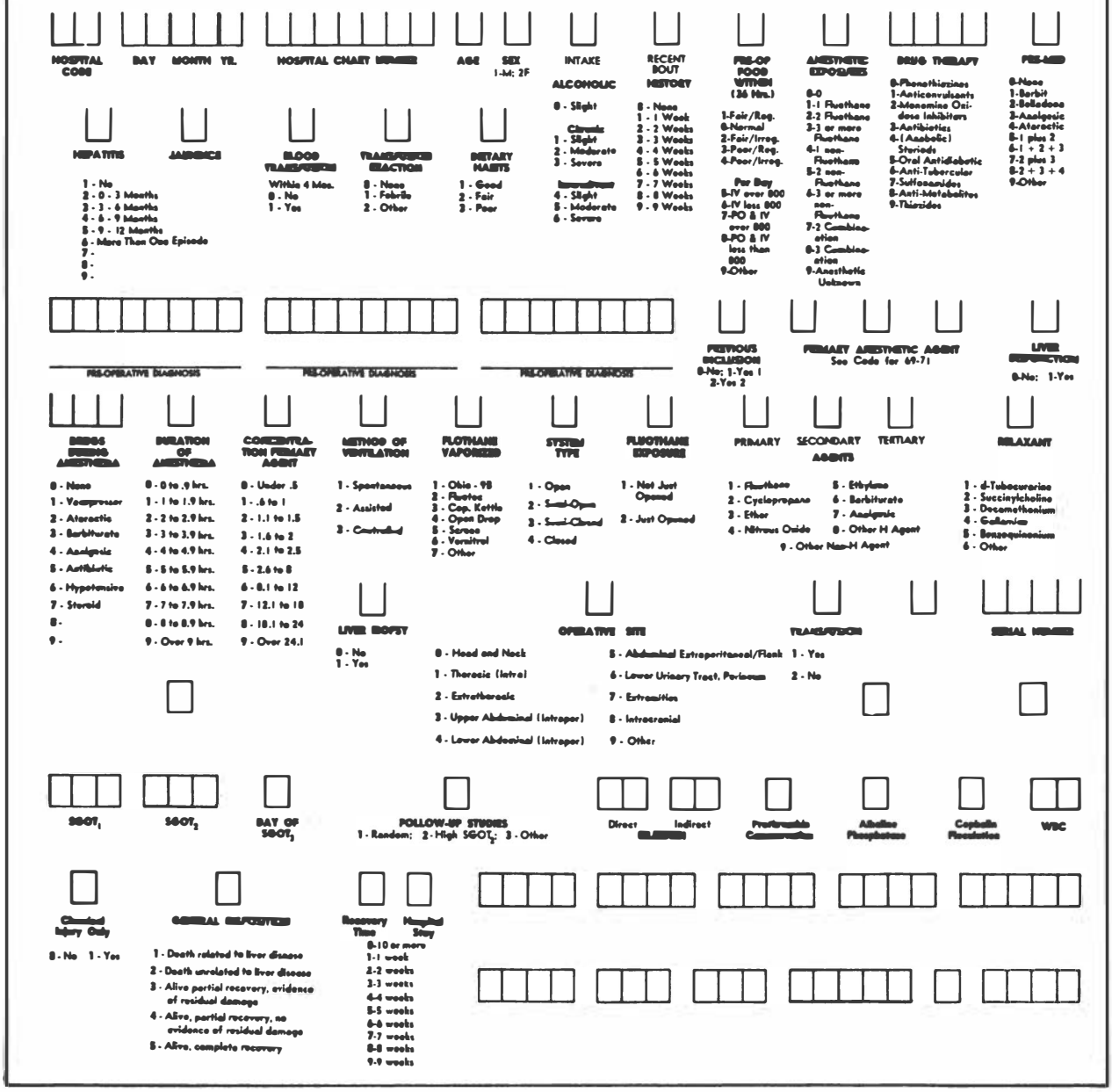

Figure 1 (Cont'd)

CHAPTER II-2. THE PROTOCOL FOR THE NATIONAL HALOTHANE STUDY

(Including a Discussion of the Problems of Data Collection)

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When attention turned from a prospective study to a study of past data, an entirely new protocol had to be written and new forms had to be designed. In developing the protocol, it was necessary to determine: (1) the kinds of data to be collected, (2) the number of cases to be reviewed, and (3) the period to be covered. To expedite the collection of a large mass of information, forms for transfer of data to Hollerith cards had to be designed. And finally, to maximize the possibility of the successful use of the protocol and forms, questionnaires were prepared to evaluate the pilot collection of data.

DEVELOPMENT OF PROTOCOL

Selection of Variables

The most difficult problem in the development of the protocol was the selection of the variables on which data were to be collected. To ensure that large-scale data collection would be kept simple and manageable, all pertinent variables were listed and then rated according to:

(1) need--the value of each variable in answering the null hypotheses,
(2) probability--the probability that the information was in the chart (missing data would create difficult problems in subsequent statistical analysis), and
(3) ease--the ease with which the variable could be found in the chart (in a review of 50,000 to 60,000 charts, simplicity is vital to ensure accuracy and completeness).

From these ratings, the variables of highest aggregate score were selected. Except for physical status and duration of anesthesia, both of which rated high in need (1) and ease (3) but low in probability (2), the plan for selection of variables was rigidly followed and those which rated high in all three categories were chosen. The variables selected were age, sex, preoperative physical status, duration of anesthesia, anesthetic agent, operation, previous operation within 4 years, previous administration of halothane within 1 year, necropsy, and presence of massive hepatic necrosis.

Determination of Sample Size

Considering the possible low incidence of massive hepatic necrosis (MHN), it was estimated that approximately 1 million cases of general anesthesia should be studied. Even with so large a number, differences between anesthetic agents might not be detectable if the projected incidence of MHN, one in 10,000 anesthetic procedures, prevailed. (This estimate was based on the over-all use of halothane and the number of cases reported either in the literature or to the Committee.)

Period of the Study

Halothane was being used extensively as early as January 1959, so that was chosen as the starting month for our investigation. December 1962 was considered an appropriate cutoff month to avoid collecting data from the "biased era" of MHN reports.

The Pilot Study

A general format, including forms and a questionnaire, was prepared to abstract the records of all deaths and randomly selected cases and to screen necropsy records for MHN. The forms were designed for ease of completion and decoding to Hollerith cards; the questionnaire was designed to evaluate (1) the sources of information, (2) the problems of data collection, (3) the clarity of the forms and protocol, (4) the time expended to collect the data, (5) the types of employees needed, and (6) the anticipated cost. Following this format, 38 volunteer institutions each submitted pilot data for 1 month (December 1962) to the Data Collection Center. The information gathered was used to make recommendations

to the National Research Council for contractual arrangements, to improve the forms and protocol, and to delineate problems of protocol interpretation that could be discussed during site visits.

It was estimated from a time analysis that each institution could analyze the data for 1 month in 1 day, and each principal investigator was to adjust his contract and request personnel to handle the workload at that rate. A few institutions could not adhere to the protocol and withdrew; others required special considerations, but were allowed no major deviations from basic protocol. Thirty-five institutions were granted contracts and used the following protocol and forms to collect data.

PROTOCOL

Introduction

A retrospective study is one based on recorded experience. Its main advantage is its economy of effort when the event of interest is infrequent. In the present study, the event of interest is death following surgery conducted under general anesthesia. Consider a hospital with a 2 percent death rate in the 6-week postsurgical period. In a forward or prospective study, it would be necessary to analyze records for 12,000 cases to find 240 deaths. In a retrospective study, the records of 240 deaths can be studied; even if coupled with an equal number of controls, the total number of records to be analyzed would be only 480, not 12,000.

The retrospective method does, however, have some disadvantages. First, some of the desired information may not have been recorded. Second, the two groups under study, test and control (in this case, halothane and nonhalothane), may not be comparable with regard to all important variables other than the anesthetic agent. This might vitiate conclusions based on comparison of the halothane-nonhalothane ratio among the deaths with the over-all ratio in surgical cases, and whether the two groups are comparable cannot be learned by comparing only the deaths. Suppose, for example, that half the halothane deaths were males and half the nonhalothane deaths were males. This would tell us nothing about the risk of a halothane death or whether the risk varied by sex. If 30 percent of all halothane surgeries were males and 50 percent of all nonhalothane surgeries were males, then a 50 percent sex ratio among the deaths for both groups would imply that halothane caused an adverse reaction in males. In short, the comparison of the anesthetics among the deaths can be misleading unless supplemented by the study of anesthetics among representative cases that did not result in death.

The two disadvantages are being dealt with as follows:

1. The pilot study for the period December 1962 showed that the information that is required is almost always in existence and is generally accessible.
2. To identify any tendencies to use halothane in more severe cases, less severe cases, particular operations, etc., a random sample of all surgical cases is required; such a sample can not only disclose these tendencies, if present, but can also allow adjustment for them; the pilot study demonstrated that the sample drawn for the test resembled the random sample closely, and for this reason the number of randomly selected charts to be abstracted per month for the 4-year analysis has been reduced from 50 to 25.

Objectives

This study is concerned with cases in which general anesthesia was used during the period 1 January 1959 to 31 December 1962, and has two objectives:

1. To compare the incidence of massive hepatic necrosis within 6 weeks of general anesthesia with and without halothane.
2. To compare the over-all incidence of death within 6 weeks of general anesthesia with and without halothane.

Experimental Design: General Information

There are a number of serious problems in designing a clinical trial to answer the questions we are asking. The most difficult is the apparent infrequency of the complication of interest; on the basis of only scanty retrospective information, it seems most unlikely that fatal hepatic necrosis occurs more frequently than once in every 5000 cases. Thus, a very large number of surgical cases must be committed to the study in order to get even a small number of cases of fatal hepatic necrosis. A multi-institutional pooling of data from 1959 through 1962 should provide an adequate number of cases.

Two facets of the investigation are important. The protocol requires that all surgical deaths, defined for the purpose of this study as deaths that occur within 6 weeks of surgery, be recorded and the charts abstracted. It also requires that charts be abstracted of a random sample of all surgical procedures. By abstracting all surgical deaths we can obtain information on the biases that affect the distribution of necropsied deaths. For example, the acutely ill patient after halothane anesthesia who develops liver complications may be more likely to have a necropsy than the patient who did not receive halothane. Inclusion of all surgical deaths constitutes a built-in check on this possibility. Random sampling of all procedures will furnish baseline data on the use of halothane and nonhalothane anesthesia in poor risks compared with good risks, in one type of surgery compared with another, etc.; only then can valid conclusions be drawn from data concerning deaths.

The procedures are designed to yield information on the following in each participating hospital:

(1) total cases of general anesthesia with halothane and without halothane,
(2) total surgical deaths,
(3) total necropsies,
(4) types of patients given halothane and not given halothane.
(5) types of patients necropsied, and
(6) massive hepatic necrosis with halothane and without halothane.

Summary of Procedure

In order to avoid the removal of too many charts from the record room at one time, as well as to allow us to look at data on a month-to-month basis, the steps described below should be followed month by month, starting with December 1962 and working back to and including January 1959. The data should always be kept separated by month.

STEP 1 Using the surgical log or duplicate anesthesia records (or the charts themselves), count the number of general-anesthetic cases done with and the number done without halothane during the month, and complete Part A of Form I. Check anesthetic agents against patients' records later withdrawn for abstracting (Steps 5 and 6).

STEP 2 Using the surgical log or anesthetic record number, (see the detailed instructions below) select a random sample of 25 general-anesthetic cases, and list their chart number and dates of operation on Part B of Form I, regardless of final disposition of patient.

STEP 3 Obtain the charts that correspond to the cases listed on Part B of Form I.

STEP 4 Obtain the records of every hospital death for the month, and complete Form II, listing their chart numbers and dates of operation and death. It is important that all death charts for the month be reviewed so that the surgical deaths as defined in the preceding section can be set aside for abstraction. Since it will be necessary as a first step in this procedure to list all the hospital deaths for the month, we must have this complete listing on Form II.

STEP 5 Obtain the hospital chart for each death listed on Form II that occurred from the time of induction of anesthesia to within 6 weeks of a general-anesthetic surgical procedure in the same hospital.

STEP 6 Mix the hospital charts listed on Form I and the charts of those patients listed on Form II who died within the 6-week period (Step 5) and abstract each chart on Form III (mixing will aid in the uniform abstracting of deaths and survivals).

STEP 7 For each record of death abstracted on Form III that was necropsied, refer to the necropsy report and complete Form IV.

STEP 8 If massive hepatic necrosis is found in any necropsy recorded on Form IV, obtain a duplication of the relevant portions of the hospital chart and necropsy records for each case. Complete Form V and transmit it with the duplicate records to the Data Collection Center.

Detailed Instruction for Recording Data

Form I, Part A

Count all operative procedures in surgery requiring services of anesthetists or anesthesiologists in your institution during the month of the report. Exclude obstetrical experience. Count all general-anesthetic cases for the month and record whether they are halothane or nonhalothane and, in addition, record whether any other halogenated hydrocarbon was used. A halothane anesthetic is one in which halothane is used regardless of time interval or concentration. A nonhalothane anesthetic is one in which halothane is not used at all. If, because of the practice in your hospital or other circumstances, you use a combination of regional, or topical, or local with general anesthesia, these cases should be included in the total count done with general anesthesia and categorized appropriately as above.

Form I, Part B

Select randomly, month by month from the surgical log or other appropriate source, cases in which a general anesthetic has been used and list on Form I, Part B. A case is eligible for random selection if it qualifies for inclusion in Part A of this form. The procedure for random selection follows.

If you have tallied 400 or more general anesthetics for this month (Item 2, Part A, Form I), select from this month's surgical log every anesthetic chart number with a 5 in the units column and any odd number in the ten column (i.e., every anesthetic chart number ending in 15, 35, 55, 75, or 95) and enter them and the other required information on Form I, Part B. This will probably yield 20 or more charts; enter as many as possible consecutively up to 25.

If you have tallied 200 to 399 general anesthetics for this month (Item 2, Part A, Form I), select from this month's surgical log every anesthetic chart number ending in 5 and enter them and the other required information on Form I, Part B. This will probably yield 20 or more charts; enter as many as possible consecutively up to 25.

If you have tallied fewer than 200 general anesthetics for this month (Item 2, Part A, Form I), select from this month's surgical log every anesthetic chart number ending in 3 or 8 and enter

them and the other required information on Form I, part B. Enter as many as possible consecutively up to 25.

Be sure to indicate the chart number and date of operation. The information later abstracted from the chart must pertain to a specific procedure and might become confused if a given patient had more than one surgical procedure per admission.

If a chart is abstracted as a death and comes up in the random sample, it should also be included here and not omitted for any reason. If a patient has multiple procedures and his unit number is selected, he may appear more than once within the same month in the random or control sample. He should be included as many times as randomly selected or death selected and a Form III should be completed for each selection even if much of the information will be repetitious.

Form II

List all deaths for this month and complete Form II, including hospital chart number, date of death and date of operation. Obtain the records for the deaths and sort them for surgical deaths as defined under "Experimental Design: General Information." Put the charts aside for abstraction. It is imperative that all death charts be checked since the patient may be considered "medical" at the time of death even if he underwent surgery within 6 weeks during a prior admission.

Form III

Collect the randomly selected control charts (Form I, Part B) and surgical death charts for the month in question, mix them, and abstract each on Form III. Assign deaths to the month in which they occurred regardless of when the anesthetic was given.

Form III is designed so Hollerith card punching can be done directly from the form after proofreading for errors or omissions. The boxes correspond to the 80 entry columns of the Hollerith card. Specific instructions for each box or set of boxes are set forth below.

FORM III - INSTRUCTIONS

INSTITUTION'S CODE NUMBER

Each institution will be assigned a number, which should be entered as follows:

Example:

INSTITUTION'S CODE NUMBER

0	1

PATIENT'S UNIT OR CHART NUMBER

Enter the number of the chart (hospital number). Both letters and numbers can be entered directly. If there are fewer than eight characters in the chart number, leave blank spaces at the left.

Example:

PATIENT'S UNIT OR CHART NUMBER

	B	1	5	5	6	7	2

NOTE: If you are using some other number to make the random selection of charts, do not put it in here, but enter on Form I, Part B, as directed in the protocol. We may have to refer to this entry to get more information from record room when necessary.

AGE

Enter the code for the age of the patient. If the age is not recorded on the chart, enter "-" (minus or dash).

Example:

6	(Patient is 64 years old)

0 = 0 - 9	5 = 50-59
1 = 10 - 19	6 = 60-69
2 = 20 - 29	7 = 70-79
3 = 30 - 39	8 = 80-89
4 = 40 - 49	9 = 90-99

- = Missing Information

SEX

Enter code for sex of patient. If the sex is not recorded on the chart, enter "-" (minus or dash).

Example:

2	(Patient is female)

1 = Male
2 = Female
- = Missing Information

DATE OF DISCHARGE OR DEATH

Enter date of death or discharge of patient as month, day, and only the last digit of year.

Example: (Patient discharged December 3, 1962)

1	2	0	3	2
Month		Day		Year

Date of Discharge or Death

NOTE: Use zeroes to fill otherwise empty boxes in this sequence and all data box sequences. This helps us to guard against inadvertently entering digits into wrong boxes.

REASON FOR ABSTRACTION

Enter the code designating the reason for abstracting this chart.

Example:

0	(This is a death abstraction)

Reason for Abstraction

0 = Death
1 = Random

AUTOPSY

Enter the code for necropsy or no necropsy but leave this box blank if the chart was selected randomly.

Example:

Autopsy

(Patient had necropsy death abstraction)

0 = No
1 = Yes

MASSIVE LIVER NECROSIS

Enter the appropriate code for massive liver necrosis. If the diagnosis is by necropsy, record 0 or 1, whichever is appropriate. If there is a clinical diagnosis of massive liver necrosis as recorded in the death certificate, enter 2. This information should appear on the line marked "How death was signed out on death certificate." ("2" should be entered ONLY IF NO AUTOPSY.)

Example:

Massive Liver Necrosis

(Death autopsy showed massive liver necrosis)

0 = No
1 = Yes Path.
2 = Yes Clin.

CAUSE(S) OF DEATH-HOW DEATH WAS SIGNED OUT ON DEATH CERTIFICATE

Write in this item. Leave blank if random abstraction.

DIAGNOSES PERTAINING TO THIS ABSTRACTION

Write in this item; do not code.

NOTE: List only those diagnoses pertinent to this admission, i.e., the chart which you are abstracting.

OPERATION FOR WHICH THIS CHART IS BEING ABSTRACTED

Write in the operation that was performed under the anesthetic for which this chart is being abstracted. The operation may include one or many separate systems of the body but can comprise one and only one anesthetic experience. If the patient has had more than one anesthetic experience, include only that information pertinent to this abstraction. If this chart is being abstracted for death, code the last operation in the boxes marked "Operation for which this chart is being abstracted." Any previous operation should be coded in the boxes "four most recent operations and dates."

CODE OPERATION

Enter code for above operation from code list of operations in the Appendix to these instructions. The list is not intended to be complete, but is adequate for the purpose of relating anesthetic experience to operative procedures on certain body systems. Where multiple operative procedures are performed, select the major procedure from the list (with the exception related to operative code number 42).

Example: Patient had D & C 12/8/62 and abdominal hysterectomy and appendectomy 12/11/62. Both procedures might come up for random abstraction. If so, two Form III's should be completed. Find code for operation in the appendix and enter as follows:

First Form III

6	0

(D & C)

Second Form III

6	5

(Abdominal hysterectomy-appendectomy)

NOTE: The D & C would appear on the second Form III as part of the history of recorded operations.

This example does not imply that all patients with two operations need to have two abstraction form (III). THERE SHOULD BE ONE ABSTRACTION FOR EACH RANDOM SELECTION.

DATE OF OPERATION

Enter month, day, and year of surgery for which record abstraction is being done. For years, enter last digit only.

From previous example:

	CODE OPERATION	DATE OF OPERATION Month	Day	Year
First Form III	6 0	1 2	0 8	2
Second Form III	6 5	1 2	1 1	2

SAMPLE DATE

Enter month and year for which these data are abstracted. These should correspond to month and year of surgery for random abstraction, or month and year of death for death abstraction.

Example: Random abstraction for surgery of 12-08-62

1	2	2

UP TO FIVE AGENTS (ANY ORDER) USED IN OPERATION ABOVE

Enter the code number for the anesthetic agents used in the operation coded and written out above. The codes for anesthetic agents are listed on each Form III.

Example: Patient had D & C under pentothal, nitrous oxide anesthesia.

0	5	0	8						

(Up to five agents (any order) used in operation above)

01 Halothane
02 Methoxyflurane
03 Cyclopropane
04 Etc. (as on Form III)

NOTE: If more than five agents were used, circle all agents used on Form III and enter those five thought to contribute most to anesthetic state. You will notice that "local," "topical," and "other" are listed in code. When these are used in conjunction with general anesthesia they are to be listed. No chart should be abstracted, either death or random, in which the agent used was regional, topical or local, to the exclusion of general anesthesia.

ANESTHETIC LENGTH MINUTES

Enter minutes directly.

Example:

	8	8

Anesthetic Length Minutes **(1 hour 28 min)**

ANESTHETIC RISK (PHYSICAL STATUS)

Enter code as listed, first ascertaining which coding system you are abstracting and then finding proper column representing that category. Enter code representing that column. Enter "-" (minus or dash) for missing information. In either event, the code is entered in the box below.

Examples: Old System 1 2 3 (4) 5 6 7 **(Poor physical status, elective)**

Old 1	2	3	4	5	6	7
New 1	2	3	4	1E2E	3E4E	5
Code 1	2	3	4	5	6	7

[4]

Physical Status

Examples: New System 1 2 3 (4E) 5 **(Poor physical status, emergency)**

Old 1	2	3	4	5	6	7
New 1	2	3	4	1E2E	3E4E	5
Code 1	2	3	4	5	6	7

[6]

Physical Status

SERIAL NUMBER

Death and random abstractions should be serially numbered for each month and category.

FOUR MOST RECENT OPERATIONS AND DATES (LAST FOUR YEARS)

(Limit to previous surgery in your hospital.) Enter operation code number and corresponding date, one for each anesthetic experience as described previously. Look up operation code in Appendix.

Example: Patient had appendectomy 1958
Open reduction fractured humerus 1960
D & C May, 1961

					5	0			8

Operation Code **Month Date** **Year** **Operation Code** **Month Date** **Year**

Four Most Recent Operations and Dates

(Last four years) (Enter above and below)

8	5			0	6	0	0	5	1

NOTE: In many instances month will not be available - just enter year.

PREVIOUS HALOTHANE EXPOSURES

Enter the number of times the patient has previously received halothane either by history or documented record.

NOTE: If history is not recorded on the chart, we can count this as no history, realizing of course the limitation of our definition.

Example: Patient had halothane on previous admission two years ago as well as halothane for this abstraction.

1

 # Previous halothane exposures

DATES OF MOST RECENT EXPOSURES TO HALOTHANE

Enter month and year of most recent exposures to halothane (space for three entries).

Example: Halothane 1961 (month not known)
Halothane November 1962
Halothane for this abstraction

	1	1 1	2		
Month	Year	Month	Year	Month	Year

Dates of most recent exposures to halothane

FORM IV

Form IV should be completed under close supervision of the responsible investigator or one of his principal associates. Format here is quite flexible because necropsy reports vary considerably from institution to institution and within a given institution. However, complete reporting of final diagnosis is necessary.

FORM V

This form pertains to the transmittal of photostatic or otherwise duplicated copies of surgical charts of massive hepatic necrosis and to the forwarding of necropsy material. Every chart of a case diagnosed as massive hepatic necrosis at necropsy must be photostated. Include history, physical, all other progress notes, laboratory studies, and other important diagnositic studies. Delete permits, authorizations, nurse's notes, and other nonpertinent information. In addition, for all cases of massive hepatic necrosis, forward:

1. **Block of liver unstained with specification of fixing method.**
2. **If not available, send slide (s) of liver with note on how it was fixed and stained. If you desire that they be returned, so state.**

334-553 O-69—6

The slides are to be reviewed by a panel of pathologists. Please label slides or block with institution code number and name as well as month of death, chart number and necropsy number. If there were no cases of massive hepatic necrosis, send blank Form V so indicating.

Precautions in Procedure

1. **The sample of general anesthetic procedures must be drawn with the instruction and supervision of someone familiar with sampling techniques. We are prepared to provide information and service at Stanford to those who require help on random sampling techniques. After the sample is selected, its value can still be compromised by failing to obtain and abstract all the case records designated; thus, a strong effort should be made to find all designated charts.**

2. **Care should be taken to ensure that halothane and nonhalothane cases are abstracted uniformly. This will be ensured in part by the instruction to abstract as much history and preoperative information as possible before the anesthetic agent is looked up and recorded. The same caution must be exercised in interpreting the necropsy information.**

3. **If an alternate method of random selection is used, a detailed resume of your technique should be given.**

Mailing Instructions

Send each month's packet of data and other relevant material as soon as completed to:

William H. Forrest, Jr., M.D.
Sutter Hospitals Research Foundation
52nd and F Streets
Sacramento, California

Send tissue blocks or slides to:

Paul R. Glunz, M.D.
Armed Forces Institute of Pathology
Walter Reed Army Medical Center
Washington, D.C.

FORM I

National Halothane Study - NAS-NRC
November 1963

B.O.B. #68-6375
Exp. 30 June 1965

PART A: - ANESTHETIC CHOICE SUMMARY

Period covered in this report:

Month_____ **Year**_____ **Institution's Code Number**_____

1. **The total number of surgical procedures during this period was**_____
2. **The number in 1 done with general anesthesia was**_____
3. **The number in 2 known to have involved the use of halothane was**_____
4. **The number in 2 known not to have involved the use of halothane was**_____
5. **How many in 3 also involved methoxyflurane or other fluorinated hydrocarbons**_____
6. **How many in 4 involved methoxyflurane or other fluorinated hydrocarbons**_____

PART B: - LIST OF CHARTS FOR ABSTRACTION FOR SAME MONTH AND YEAR AS ABOVE

	Identifying Number - Chart or Other Number Used in Random Selection*	Date of Operation
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		

*If other than chart numbers, specify the method used in selection of numbers.

FORM II

National Halothane Study - NAS-NRC
November 1963

B.O.B. #68-6375
Exp. 30 June 1965

LIST OF HOSPITAL DEATHS

Data Collector's Name _____ **Date of Collection** _____ **Institution's Code Number** _____

All hospital deaths for (Month) _____ **(Year)** _____

Total Number of deaths: Non-Surgical _____ **Surgical** _____

Hospital Chart #	Date Death	Date Operation	Hospital Chart #	Date Death	Date Operation

FORM III

National Halothane Study - NAS-NRC
November 1963

B.O.B. #68-6375
Exp. 30 June 1965

ABSTRACTOR'S NAME_____

INSTITUTION'S CODE NUMBER ☐☐

PATIENT'S UNIT OR CHART NUMBER ☐☐☐☐☐☐☐☐

☐ AGE	☐ SEX	☐☐ Month ☐☐ Day ☐ Year	☐ Reason for Abstraction	☐ Necropsy	☐ Massive Hepatic Necrosis
0 = 0-9 1 = 10-19 2 = 20-29 3 = 30-39 4 = 40-49 5 = 50-59 6 = 60-69 7 = 70-79 8 = 80-89 9 = 90-99 - = Missing Info.	1 = Male 2 = Female - = Missing Info.	Date of Discharge or Death	0 = Death 1 = Random	0 = No 1 = Yes	0 = No 1 = Yes Path. 2 = Yes Clin.

CAUSE(S) OF DEATH-HOW DEATH WAS SIGNED OUT ON DEATH CERTIFICATE (Write above)

DIAGNOSES PERTAINING TO THIS ABSTRACTION (Write below)

1 _____ 4 _____

2 _____ 5 _____

3 _____ 6 _____

OPERATION FOR WHICH THIS CHART IS BEING ABSTRACTED (Write below)

_____

CODE OPERATION ☐☐

DATE OF OPERATION Month ☐☐ Day ☐☐ Year ☐

SAMPLE DATE Month ☐☐ Year ☐

☐☐ ☐☐ ☐☐ ☐☐ ☐☐

(Up to five agents (any order) used in operation above)

01 Halothane	05 Nitrous Oxide	10 Surital	14 Relaxant	18 Topical
02 Methoxyflurane	06 Trilene	11 Other Barb.	15 Spinal	19 Fluomar
03 Cyclopropane	07 Ethylene	12 Narcotic	16 Epidural	20 Vinethene
04 Ether	08 Pentothal	13 Antagonist	17 Local	21 Other
	09 Brevital			

FORM III (Cont'd)

Anesthetic Risk

Old	1	2	3	4	5	6	7
New	1	2	3	4	1E2E	3E4E	5
Code	1	2	3	4	5	6	7

☐

Anesthetic Length Minutes ☐☐☐

(Leave Blank) ☐☐☐☐☐☐

☐☐ **Operation Code** ☐☐☐ **Month Year Date**

☐☐ **Operation Code** ☐☐☐ **Month Year Date**

***FOUR MOST RECENT OPERATIONS AND DATES --- (Last four years) (Enter above and below)**

Operation Code ☐☐ **Month Year Date** ☐☐☐

Operation Code ☐☐ **Month Year Date** ☐☐☐

☐ **#Previous halothane exposures** ☐☐☐ **Month Year**

☐☐☐ **Month Year**

☐☐☐ **Month Year**

Dates of most recent exposures to halothane

***LIST BELOW THOSE OPERATIONS NOT CODED IN APPENDIX AND DATES**

FORM IV

National Halothane Study - NAS-NRC
November 1963

B.O.B. #68-6375
Exp. 30 June 1965

ABSTRACT OF NECROPSY REPORT

Hospital Chart #_____ Necropsy #_____ Institution's Code #_____

Abstractor's Name_____

LIVER

(Check one if applicable)

- ☐ **Massive Hepatic Necrosis**
- ☐ **Focal Hepatic Necrosis**
- ☐ **Other Hepatic Disease(s)**

List final necropsy diagnosis

FORM V

National Halothane Study - NAS-NRC
November 1963

B.O.B. #68-6375
Exp. 30 June 1965

Necropsy Information for Cases of Massive Hepatic Necrosis:

Period Covered in this Report:

Month _____ **Year** _____ **Institution's Code Number** _____

Number of cases of massive hepatic necrosis _____

List of Pertinent Clinical and Necropsy Records Forwarded to Computation Center

Chart #	Necropsy #	Date of Death	No. of Pages of Records

List of Necropsy Specimens Forwarded to Armed Forces Institute of Pathology

Chart #	Necropsy #	Date of Death	Specimen(s) - specify block, slide(s) or both

APPENDIX

National Halothane Study - NAS-NRC
November 1963

OPERATION CODES

Head and Neck:

01 Mouth, dental, T&A, tongue, lymph node biopsy (head-neck), myringotomy
02 Nose all, s.m.r., fracture
03 Eye all
04 Ear all, except myringotomy
05 Radical neck
06 Fracture, maxilla, mandible, excision or biopsy
07 Exocrine biopsy or excision
08 Excision embryonic remnants
09 Neck, cervical sympathectomy, resection of 1st rib
10 Thyroid, all
11
12 Craniotomy
13 Burr holes, only, ventriculogram
14
15 Pneumoencephalogram
16 Arteriogram, aorta or major vessel, cardiac catheterization
17 Carotid artery endarterectomy, graft
18
19
20 Endoscopy-trachea, esophagus, larynx
21 Endoscopic excision biopsy, trachea, esophagus, larynx
22 Tracheostomy
23 Laryngectomy
24
25

Thorax:

26 Lung biopsy
27 Lung, all except biopsy
28 Hiatus hernia, transthoracic
29
30 Breast biopsy, abscess, simple mastectomy
31 Mammoplasty
32 Radical mastectomy
33 Heart and great vessels, pump
34 Heart and great vessels, no pump
35
36 Mediastinum, all
37
38

Abdomen, Gastro-Intestinal:

39 Hiatus hernia (abd. approach)
40 Cholecystectomy, alone
41 Cholecystectomy and bile ducts
42 Cholecystectomy with other major procedures*
43
44 Expl. lap., biopsy, lysis of adhes.
45 Gastric resection, pyloroplasty, vagotomy
46 Close ruptured ulcer
47 Small bowel, all
48 Large bowel, all
49
50 Appendectomy
51 Abdominal perineal resection
52 Closure evisceration
53
54 Hemorrhoidectomy and sigmoidoscopy
55 Herniorrhaphy, incisional, umbilical, inguinal, femoral, ventral
56
57 Large vessel surgery, graft endarterectomy
58 Sympathectomy, bilateral adrenalectomy
59 Splenectomy, partial hepatectomy, pancreatectomy, porto-caval shunt, spleno-renal shunt

Female:

60 D&C, bartholin cystectomy, culpotomy, insertion radium, cervical biop.
61
62 Caesarian section
63 Ectopic pregnancy
64
65 Hysterectomy, all including bilateral salpingo-oophorectomy, or other variation of hysterectomy, such as A&P repair
66 Pelvic laparotomy, adhesion, suspension, oophorectomy, salpingectomy, cystectomy
67 Radical pelvic exenteration
68 A&P colporrhaphy
69

Male:

70 Prostate, t.u.r., biopsy, suprapubic, retropubic
71 Hydrocoele, orchiectomy, circumcision
72

Urinary Tract:

73 Cystoscopy, retrograde, fulgeration, bladder tumor
74
75 Kidney, all
76 Ureter, all, ureterolithotomy
77 Bladder, all except electric fulgeration
78
79

*For combined procedures the major procedure should be selected except for those cases which have a cholecystectomy as part of the procedure, and for these use Code 42.

APPENDIX--Continued

OPERATION CODES--Continued

Extremities:

80 Fractures, all closed reduction
81 Muscle, fascia, tendon, nerve surgery, neurorrhaphy
82
83
84 Joints, open all
85 Open reduction, all bones except femur
86 Open reduction, femur
87 Amputations, fingers, toes
88 Amputations, hand, upper extremity, foot, lower extremity
89 Saph. vein lig. and strip.

Skin and Miscellaneous:

90 Plastic surgery, skin only, debridement, biopsy, excision small lesions.
91
92 Minor procedures miscellaneous
93 Major procedures, miscellaenous
94
95 Pilonidal I&D or excision, I&D abscess superficial
96
97
98 Laminectomy, cervical
99 Laminectomy, thoracic, lumbar

NOTE: IF YOU CANNOT FIND THE OPERATION IN THE APPENDIX WHICH YOU HAVE WRITTEN ON FORM III THEN LEAVE THE CODE AREA BLANK. UNDER "FOUR MOST RECENT OPERATIONS" WRITE IN AT THE BOTTOM OF FORM III THOSE YOU CANNOT FIND IN APPENDIX.

Addenda to Protocol

Addendum I (June 1964):
Implementation of Collection and Review of Pathology Data - National Halothane Study

Personnel of the Data Collection Center are to review all Form IVs (Necropsy Summaries) to check for consistency of the coding of massive hepatic necrosis. The necropsy information is to be divided into the following categories: massive necrosis, possibly massive necrosis, other necrosis, fatty metamorphosis, hepatitis, other liver disease and no liver disease. All cases categorized as massive, possibly massive and hepatitis not already submitted will be requested. A critical review of the submitter's diagnoses compared to the categories of this sort will be made.

Addendum II (August 1964):
Implementation of Collection and Review of Pathology Data - National Halothane Study

All necropsy summaries except those where no mention is made of the liver are to be reviewed by a consultant pathologist for any suggestion that the liver may have played a role in the patient's death; in such case, a photostatic copy of the complete necropsy report will be requested and reviewed. The morphologic description of the liver will be examined for evidence of necrosis where no specific diagnosis was made. Slides will be requested on all cases of hepatic necrosis of any degree.

Another consultant pathologist will review the above requested slides and set aside for the Panel's review cases with submassive or massive necrosis of the liver. Cases with infarcts (single or multiple), necrosis in relation to tumors (primary or secondary), and focal or local necrosis associated with liver infections, peritonitis or other diseases are to be excluded. Also, livers showing fatty metamorphosis, collapse and scarring in the absence of necrosis, and livers showing marked degrees of autolysis are to be excluded. Special attention is to be paid to autolyzed livers in which the diagnosis of submassive or massive necrosis could be made in spite of the postmortem degeneration. These cases should be included for Panel review even though a detailed study of the type of necrosis may not be possible because of the postmortem autolysis.

The cases selected from the above review are to be submitted to the Pathology Panel for completion of Form VI only. Chart abstracts will be completed for these cases also.

An abstract of the chart of all patients suspected of massive hepatic necrosis will be prepared for subsequent review by pathologists. Forms VIII and IX were prepared to make the clinical information easily retrievable.

Addendum III (August 1964):
Preparation and Distribution of Hepatic Necrosis Slides - National Halothane Study

Massive hepatic necrosis blocks will be prepared into slides of three in a set and will be distributed one set to each of the pathologists.

Massive hepatic necrosis slides (no blocks submitted) will be appropriately numbered and grouped concurrently to be sent as a "round robin" amongst the pathologists.

Addendum IV (August 1964):
To Facilitate Analysis of Results of the Review of Liver Slides by Pathologists - National Halothane Study

In order to facilitate analysis of the results of the review of the liver slides by the Pathology Panel, Forms VI and VII are to be designed and the following protocol established. Each pathologist will review slides suspected of massive hepatic necrosis and complete Form VI (morphologic description). Each pathologist is to submit the Form VIs to the Data Collection Center in Sacramento. Upon receipt of the Form VI, the Data Collection Center will send to the pathologist a chart abstract that corresponds to the slide reviewed on the Form VI. The pathologist will review the chart abstract and the slide and complete Form VII.

All of the above review by the Pathology Panel will be done without knowledge of anesthetic agent.

Addendum V (May 1965):
To Facilitate Analysis of Results of the Review of Liver Slides by Pathologists - National Halothane Study

A consultant pathologist will review all originally submitted slides of massive hepatic necrosis and exclude from consideration those cases not qualifying to criteria established in Addendum II.

NATIONAL HALOTHANE STUDY FORM VI

STUDY CASE #_____ I. LOBULAR CHANGES

	DEGREE[1]
1. PRE-EXISTING LOBULAR ARCHITECTURE	
NORMAL _____ ABNORMAL _____	
2. AUTOLYSIS[2] _____	
3. NECROSIS _____	
LOCALIZATION — TYPE	
CENTRAL _____ COAGULATIVE _____	
PARACENTRAL _____ LOSS OF CELLS _____	
MIDZONAL _____ ACIDOPHILIC BODIES ____	
PERIPHERAL _____	
FOCAL _____	
INDETERMINATE	
4. CYTOPLASMIC VACUOLIZATION:	
FATTY _____	
LARGE _____	
SMALL _____	
OTHER: SPECIFY _____	
_____	
PSEUDOXANTHOMA CELLS _____	
5. PIGMENTATION	
HEPATIC CELLS: LIPOFUSCIN _____	
IRON _____	
BILE _____	
KUPFFER CELLS: LIPOFUSCIN _____	
IRON _____	
BILE _____	
FORMALIN: _____	

NOTE:
[1] Grade "DEGREE" from 0-4+ where applicable.
[2] When "AUTOLYSIS" precludes evaluation the form need not be completed.

FORM VI (Cont'd)

STUDY CASE #_____

	DEGREE
6. INFLAMMATION	
NECROTIC AREAS	
DIFFUSE	
FOCAL	
NON NECROTIC AREAS	
DIFFUSE	
FOCAL	
CELL TYPE:	
POLYS	
LYMPHS	
EOS	
HISTO	
7. BILE STASIS	
CENTRAL	
PERIPHERAL	
DIFFUSE	
LAKES	
8. REGENERATION	
9. CENTRAL VEIN ENDOPHLEBITIS	

II. PORTAL TRIADS	DEGREE
1. INFLAMMATION	
ALL PORTAL AREAS	
SCATTERED PORTAL AREAS	
CELL TYPE:	
POLYS	
LYMPHS	
EOS	
HISTO	
2. BILE STASIS	
DUCT	
DUCTULE	
3. SCARRING	
4. DUCTULE PROLIFERATION	

NATIONAL HALOTHANE STUDY FORM VII

STUDY CASE # _____

A. **Taking into account the clinical features and necropsy findings in this case, the histologic changes in the liver can be attributed to:**

1. **A single specific etiologic factor** _____
2. **The combined effects of multiple etiologic factors** _____
3. **Any one of several etiologic factors** _____

or

4. **Do not warrant any etiologic diagnosis** _____

B. **The histologic changes in the liver are consistent with the effects of:**

1. **Halothane** _____
2. **Any hepatotoxin** _____
3. **Any drug-sensitization reaction** _____
4. **Hepatitis virus** _____
5. **Shock, anoxemia and/or sepsis** _____
6. **Any other etiologic factor specify:** _____

or

7. **Do not warrant any specific etiologic diagnosis** _____
8. **Cannot be interpreted because of postmortem autolysis** _____

_____
PATHOLOGIST

NATIONAL HALOTHANE STUDY FORM VIII

CHART ABSTRACT

II. SPECIFIC SURVEY FOR HEPATIC DISORDERS:

Known Liver Disease (prior to surgery) Yes_____No _____Unknown _____
- Diagnosis:
- Jaundice:
- Hepatomegaly:
- Hepatic Tenderness:
- Other

Alcoholism Yes_____ No _____Unknown _____
- Amount:
- Type:
- Duration:
- Other comments:

Hepatotoxic exposure Yes_____No_____Unknown_____
- Type:
- Duration:
- Comment:

Homologous serum hepatitis, possible exposure Yes_____No_____Unknown _____
- Dental work under local:
- Injections during preceding 6 months:
- Blood transfusions: (prior to hospitalization)
- Tattoos:
- Other:

Right-sided cardiac failure: Yes_____No_____Unknown_____
- Etiology:
- Duration:
- Severity:
- Response to therapy:
- Time relation to surgery:
- Other:

Allergies: Yes_____No_____Unknown _____

Drug or agent	Type of reaction	Last exposure

NATIONAL HALOTHANE STUDY FORM IX

CHART ABSTRACT

III. CLINICAL COURSE

POSTOP: The chart has been reviewed for the below listed signs and symptoms. If present, the date of onset, duration of episode and other comments will be found on the following page.

	YES	NO	UNKNOWN
Rash	____	____	____
Fever	____	____	____
Chills	____	____	____
Ascites	____	____	____
Hypotension	____	____	____
Shock	____	____	____
Peripheral cyanosis	____	____	____
Cardiac failure	____	____	____
Edema	____	____	____
Hepatomegaly	____	____	____
Jaundice	____	____	____
Hepatic tenderness	____	____	____
Hepatic encephalopathy	____	____	____
Purpura	____	____	____
Bleeding	____	____	____
Hematuria	____	____	____
Splenomegaly	____	____	____
Anemia	____	____	____
X-rays	____	____	____

PROBLEMS OF DATA COLLECTION

Each step of the final protocol (dated January 1964) was clearly outlined and forms were provided to simplify data collection, as well as transcription to Hollerith cards. A review of the methods used in each institution, deviations from protocol, and evaluation of data collection and missing data are presented in the following paragraphs.

Monthly Totals

There were five sources of information for a total count of surgical cases done under general anesthesia. Of the 35 institutions, 26 used the surgical log, two used the anesthetic log, two used Hollerith records, one used McBee punchcards and records, and four used the original records of each anesthetic administration.

To check the accuracy of the information transferred from anesthetic records to the logbook and thus the accuracy of total count, it was suggested in the protocol that each selected random (Form I, Part B) be compared with the information source of the total count (logbook). In practice, this check was cumbersome and time-consuming, so the principal investigators were asked to compare the randoms for September of each year with the surgical or other log. This was done after the September data were submitted, by returning a list of the random cases (Form I, Part B) for that month to the principal investigator and requiring him to record the anesthetic agent that appeared in the log corresponding to the particular chart numbers. In some institutions, other methods of checking were used, and in others, more frequent checks were made. Most institutions found very few errors in the log; a few discovered as many as eight in 1 month. In view of (1) errors in the original transcription of the anesthetic agent from the anesthetic record to the log, which would naturally lead to some discrepancies between what was used and what was reported in Form I, Part A, and (2) more importantly, the absence of total counts of anesthetic agents other than halothane, it was decided that the administration rates of all agents would be estimated from the random selection.

After all 48 monthly counts (Form I, Part A) were recorded on Hollerith cards, they were listed for each institution and hand-checked for inconsistencies. Indications of possible errors were found in two hospitals, on the basis of apparent inconsistencies in the totals. A check on this revealed that one institution had no counts for January through April 1959, because it had not opened until May 1959, and another had moved to a smaller operating-room suite during the Study.

Missing data were not a problem with regard to Form I, Part A.

Random Selection

Depending on the number of general anesthetics administered in a particular month, randoms were selected using the patients' chart numbers, anesthetic chart numbers, or surgical log numbers, by choosing an appropriate 10 or unit digit calculated to yield 25 randoms per month. These earmarked charts were selected in chronologic order from the log until 25 cases with general anesthesia were collected or the list was exhausted. Of the 32 institutions that followed this method, 10 (institutions 2, 8, 9, 13, 14, 16, 25, 27, 29, and 34) used other than chart numbers; therefore, their random chart numbers did not show a pattern that would indicate the method of selection.

Missing Charts

The random selection listing (Form I, Part B) was checked to ensure that no eligible charts were overlooked. (The protocol required a listing of all eligible randoms, whether or not they could be found and submitted; adherence to this requirement was a subject for special attention during site visits.) When a chart was tallied as missing, the Data Collection Center asked for a search of records. If the chart was unavailable, every effort was made to secure information from duplicate anesthetic records, surgical logs, death certificates, and pathology reports. Several institutions had a high incidence of missing charts in the initial selection; but, through excellent cooperation and persistent follow-up procedures, many of these charts were retrieved (Table 1), so that only a very few were missing in the final tally.

Frequently, there were no missing random charts but the number of randoms did not reach 25 per month, primarily because it was difficult to estimate the number of rejects (regional and local anesthetics) that would be encountered among the designated cases. There were 19 institutions with fewer than the maximum of 25 for

TABLE 1.--MISSING RANDOM CHARTS

Institution	No. randoms submitted	Missing charts No.	Missing charts %	Estimated administrations
11	1,113	1	0.09	26,255
13	1,122	5	0.45	6,892
14	1,123	15	1.34	27,085
15	1,166	12	1.03	30,273
16	1,194	3	0.25	16,097
20	1,207	2	0.17	47,610
25	1,137	12	1.06	8,447
27	1,131	5	0.44	27,259
28	1,057	13	1.23	7,063
30	786	2	0.25	4,398
33	1,199	1	0.08	26,825

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some months but with no missing randoms (institutions 4, 5, 6, 7, 8, 9, 10, 12, 17, 18, 19, 21, 23, 24, 26, 29, 31, 32, and 35).

Departures from Protocol for Random Selection

Acceptable Deviations

Institution 3 used the surgical log and chose every 20th patient. If a regional anesthestic was encountered, the preceding record was chosen. Institution 21 used a different system of digits each month as the basis for selection from December 1962 to June 1962 (data were collected for the most recent month, December 1962, and then in reverse order for each preceding month); protocol procedures were then used for the remainder of the Study period. Institution 27 serially numbered the surgical log and selected all numbers that ended in 5.

The deviations from protocol permitted for institutions 3 and 27 were considered of minor importance. Institution 21 deviated in a manner that could conceivably introduce bias if the selection of numbers was based on some preconceived notion about the data to be abstracted.

Unacceptable Deviations

The following deviations were considered unacceptable:

(1) omission of an earmarked random chart for any reason (i.e., chart not available),
(2) submission of more than 25 random charts, and
(3) replacement of a missing chart with another.

Selection of Deaths - Form II

The hospital death list, usually kept in the record room, was the source of the death selection. The protocol stipulated that all hospital deaths be recorded on Form II and that all death charts be read to determine which met the protocol requirement, i.e., death within 6 weeks of the administration of a general anesthetic. The major difficulty in adherence to the protocol in this phase was again the location of missing charts. The importance of including the entire death list on Form II was emphasized in the protocol, and presumably no hospital deaths that followed general anesthesia could go undetected. However, it was often difficult to locate missing charts and, although there was excellent follow-up and every reasonable attempt was made to find missing charts, many were not found. Attempts to categorize missing charts by searching other documents, such as death certificates and necropsy protocols, were usually not fruitful.

There were nine institutions with missing death charts (Table 2). In two (14 and 35), enough charts were missing to make the validity of any data on death or MHN derived from them questionable. By examining Form II and establishing the ratio of surgical to nonsurgical deaths in each hospital over the entire 4-year period, we could estimate the number of missing surgical charts. Thus, for institution 14, it was estimated that four of the 35 missing death charts were probably surgical; and for institution 35, 75 of the 187 missing death charts were probably surgical. To avoid errors in estimating the death rates, an upper limit of 5 percent missing surgical death charts was established; therefore, the data for institution 35 were not included in the statistical analysis.

TABLE 2

Institution	Missing death charts: Over-all	Missing death charts: Estimated surgical	Total deaths in study	Percent death charts missing
11	9	2	555	0.4
13	1	0	246	0.0
14	35	4	141	2.8
15	7	1	586	0.2
16	1	0	519	0.0
20	1	0	727	0.0
25	10	1	578	0.2
30	2	0	223	0.0
35	187	75	1,348	5.6

Random and Death Abstractions - Form III

All selected random and death charts were abstracted to complete Form III. Missing information was accounted for by appropriate coding to avoid confusion with blank spaces for data not yet entered. To ensure accurate over-all categorization and identification of all Form IIIs, they were checked manually for correct coding of institution, month, year, and operation. The data were then transferred to Hollerith cards, verified, and checked for error by programs developed to find inconsistencies, omissions, and errors more quickly and accurately. Frequent communication between the Data Collection Center and the principal investigator made it possible to correct most of the errors.

A code for operations was developed that was simple to use and would not require highly trained personnel or complicated codes, such as the International Classification of Diseases and Operations. Categorization based on regional site was most important in the development of this code. Unassigned codes were available in case additional classifications for operation were needed during the Study. All institutions were urged to leave columns 21-22 (operation code) blank if they were not sure of the code for a specific operation. By sorting all the uncoded Form IIIs and having one person code them at the Data Collection Center, it was possible to obtain consistency of coding for the less-common operations. If one type of operation frequently appeared uncoded, a code was assigned and all participants were notified by means of a flyer.

Evaluation of Missing Data and Errors - Form III

Manual and programed computer checks revealed many errors and omissions, which the appropriate institutions were asked to correct. The general response to such requests was excellent and most of the elusive data were retrieved. Many institutions had difficulty in locating charts for abstraction, and it was obviously much more of a problem in some institutions than in others. The number of missing charts may have reflected management problems in the record room, but it appeared more likely to have reflected conditions in an active center where charts were in constant circulation.

Selection of Massive Hepatic Necrosis Cases - Forms IV, V

Necropsy protocols, summaries, or both were examined by the principal investigators or their designated assistants for evidence of MHN. In the pilot study it was often difficult or impossible to assess the degree of necrosis from the information on the necropsy protocols. For instance, in reviewing a necropsy protocol, it was difficult to state whether the recorded information, such as "marked centrilobular necrosis," actually represented massive hepatic necrosis. To help the principal investigators make judgments and to provide data for later evaluation of judgments, we advised them to include a summary for each necropsy and to be liberal in their interpretations of MHN so that all borderline cases would be submitted for review by the Pathology Panel.

All cases of MHN (as determined by the principal investigators) were reported on Forms III, IV, and V. Investigators were urged during site visits to select MHN cases without knowledge of anesthetic agent if possible. It was hoped that there would be minimal bias in MHN reporting, but actually the agent was known about half the time. A copy of the chart of every MHN case was submitted to the Data Collection Center, and a block of tissue and microscopic slides of the liver were submitted to the Armed Forces Institute of Pathology (AFIP) in Washington, D.C.

DATA EVALUATION AND EXTENSION OF PATHOLOGY PROTOCOL

Evaluation of Form IV

Review of Form IV for consistency of chart numbers, necropsy numbers, and correlation with reports of degree of necrosis in Form III, column 19, was not difficult and was rewarding. It became apparent that there were occasional discrepancies in the extent of hepatic disease reported in the necropsy summary (body of Form IV), the classification of hepatic disease at the top of Form IV, and the indication that necrosis occurred as recorded in column 19 of Form III. This and similar inconsistencies led to a complete review of the Form IV information.

All necropsy information provided on Form IV was reviewed at the Data Collection Center, without knowledge of the anesthetic, in an effort to detect overlooked MHN. Cases not previously submitted but possibly representing massive or submassive necrosis or hepatitis were sought from participating institutions.

Pathology Review of Form IV and MHN Slides

To investigate discrepancies in the reports on Form IV, as delineated by the review of a major portion of the Form IVs submitted, the Subcommittee amended the protocol (Addenda III and IV). It also commissioned two consultant pathologists (1) to review the information on Form IV from all the necropsy reports, except those which did not mention the liver, and sort out and request microscopic slides on all cases in which hepatic necrosis could have been present, and (2) to review these slides and sort out cases in which there were appreciable degrees of MHN. These, along with original slides, were then handled as described below.

Handling and Circulation of MHN Slides

All material sent to AFIP was prepared for circulation to the Pathology Panel. When enough material was submitted, sets of slides were prepared for each pathologist so that each set contained material stained with standard techniques and unstained sections for special staining. Unfortunately, not all material sent to AFIP was in the form of blocks; in some cases, only one slide that had been prepared at the investigating institution was available.

Protocol for Review of Bona Fide Cases

As the MHN charts for abstraction and the hepatic slides for review became available, it was obvious that addenda to the protocol were essential to standardize the Panel's review of the slides and chart abstracts and to provide forms for recording this information. In addition, four new forms (VI through IX) were designed to record the Pathology Panel's morphologic description of the hepatic slides and etiologic factors in the cause of the heptatic necrosis. The forms were also used to record, in tabular fashion, the data from the chart abstractions, and to outline the general format of the chart abstractions.

Microscopic sections from all cases were examined by the five members of the Pathology Panel. The extent of necrosis was rated by each pathologist independently on a scale of 0 to 4. These ratings were averaged and the cases were separated into three categories: (1) massive necrosis (average score, 2.6 or above), (2) intermediate necrosis (average score, 1.6 to 2.5), and (3) minimal necrosis (average score, 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. Assignment of necrosis and description of morphology were made without knowledge of anesthetic or clinical history.

On receipt of Form VI at the Data Collection Center, an abstract of the corresponding clinical history, from which the identity of the anesthetic agent was deleted, was sent to each pathologist. The Pathology Panel then reviewed the slides with access to the chart abstracts that were prepared according to Forms VIII and IX and included all clinical factors of importance except the anesthetic agent. Only the office copy included the anesthetic agent. The purpose of the second review was to elicit opinions from each member of the Pathology Panel as to possible or probable etiology of the observed hepatic necrosis as required by Form VII.

Review of Form VI and Protocol Addendum

Slides from approximately 100 cases scored by all five pathologists (Form VI) were reviewed for consistency of scoring and evaluation of scoring technique. In all but 11 of the first 100 slides reviewed, consistency of scoring was good; there were only few instances of a spread of more than one degree of necrosis. In 11 cases, however, there was considerable inconsistency in scoring; scores ranged from 0 to 4 or, in some cases, slides were not interpretable owing to autolysis. The morphologic description and the necropsy summary reports on these 11 cases were examined, and it was found that such factors as necrosis near malignant tissue or abscess and marked autolysis accounted for the discrepancies in the scoring. The pathologist who had already been commissioned to review the additional slides (solicited in Addendum IV) was designated to screen the original MHN cases to eliminate those in which there was marked autolysis or other interfering variables.

Problems of Pathology Data Collection

Except for the coding of necrosis, it was difficult to obtain consistency in coding the pathology forms. Variables were frequently not coded, indicating either an absence of the variable or missing information. No means were found in the protocol to detect these differences.

Missing Pathology Data - Charts and Slides

Slides Submitted by Principal Investigator

Six cases of necrosis were reported for which no slides were submitted; two involved cyclopropane, one ether, and three Other.* In three cases the wrong tissue was submitted and no substitute tissue was available; two involved cyclopropane and one thiopental-nitrous oxide. In two cases slides were lost and not replaced; both involved cyclopropane.

Slides Requested by Pathologist Consultants

Twenty-six slides that were requested on the basis of review of necropsy summary could not be obtained; two involved halothane, 11 thiopental-oxide, five cyclopropane, and eight Other. For four slides requested and obtained for review, corresponding clinical charts were never obtained; two were scored as massive hepatic necrosis (one involved thiopental-nitrous oxide and one ether), and two were scored as intermediate necrosis (both involved thiopental-nitrous oxide).

*For comparisons, anesthetic agents were separated into the following anesthetic practices: (1) halothane, (2) nitrous oxide-barbiturate, (3) cyclopropane, (4) ether, and (5) "Other." These categories are described more fully in Appendix 1 to Chapter IV-2.

PART III. REPORT ON HEPATIC NECROSIS

CHAPTER III-1. OVER-ALL RESULTS OF THE STUDY OF HEPATIC NECROSIS

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This chapter describes the data on massive hepatic necrosis. It also includes discussion of some of the limitations of interpretation due to problems in the collection of necropsy data; tables relating such variables as operation, age, and institution to incidences of massive hepatic necrosis; and descriptions of special studies attempting to determine the etiology of massive hepatic necrosis. Subsequent chapters in Part III deal with interpretation in more detail, including the Pathology Panel's review of massive hepatic necrosis, the statistical analysis of hepatic data, and the clinical syndromes associated with postoperative hepatic necrosis.

TABLE 1*.--COMPARISONS OF ANESTHETIC PRACTICE BY YEAR
(PERCENTAGE DISTRIBUTION)

Year	Anesthetic practice**					Estimated total administrations
	Hal	N-B	Cyclo	Ether	Other	
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
Percent of 4-year total	29.8	25.5	17.2	11.9	15.6	
4-Year total	254,896	218,221	147,358	102,014	134,026	856,515

*In this and subsequent tables, numbers may vary and may not add to their totals because of rounding.

**For comparison, anesthetic agents were separated into the following anesthetic practices: (1) halothane (often abbreviated as "Hal"), (2) nitrous oxide-barbiturate ("N-B"), (3) cyclopropane ("Cyclo"), (4) ether, and (5) Other. Combinations of halothane, cyclopropane, and ether were placed in the "Other" category. General anesthetics not included in the first four classes were also classified as "Other."

NECROPSY RATES AND THE IMPLICATIONS OF MISSING NECROPSY INFORMATION

Necropsy Rates

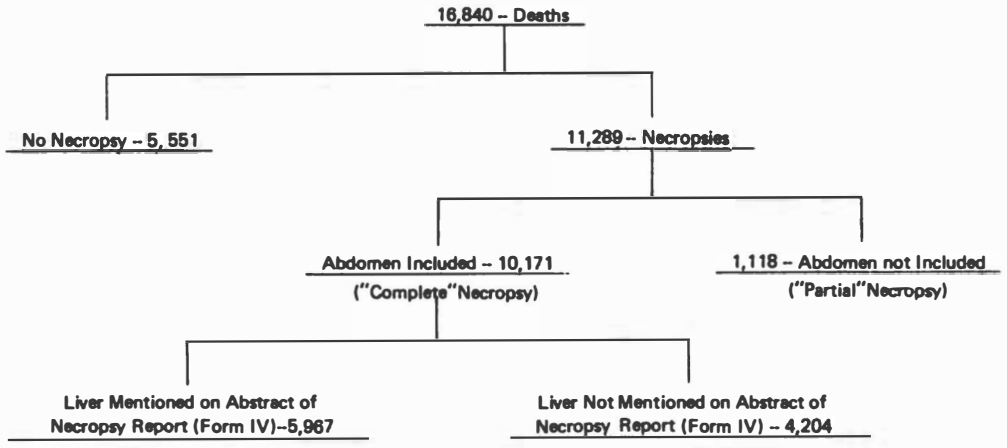
During the 4-year period of study, general anesthetics were administered approximately 856,500 times in the 34 participating institutions (Table 1).

Records of 16,840 deaths were examined during the Study. In 11,289 of these, necropsy had been performed, and in 10,171 cases, necropsy included examination of the abdomen (Fig. 1). Necropsy including the abdomen will be referred to as "complete," and necropsy excluding the abdomen will be referred to as "partial."

The over-all rate* of complete necropsies was 60.4 percent (Table 2); it varied from 31.3 percent (institution 23) to 88.3 percent (institution 30). The over-all rate of partial necropsies was 6.6 percent, with a range among institutions of 0 to 25.7 percent (institutions 34 and 32, respectively). The rate of partial necropsy among the five anesthetic practices varied from 2.7 to 9.3 percent; this wide range is probably related

FIGURE I

NECROPSY CLASSIFICATION



*Rates for complete and partial necropsies are based on total deaths.

TABLE 2.--NECROPSIES BY ANESTHETIC PRACTICE AND INSTITUTION

Inst.	Hal			N-B			Cyclo			Ether			Other			Total		
	P	C	D	P	C	D	P	C	D	P	C	D	P	C	D	P	C	D
1	12	80	189	2	17	55	0	5	7	0	4	5	3	12	38	17	118	294
2	0	93	226	0	44	94	4	77	177	0	11	22	1	45	95	5	270	614
3	3	17	25	6	52	106	0	15	20	0	1	1	0	32	49	9	117	201
4	13	54	105	7	47	98	10	118	223	2	62	94	15	111	197	47	392	717
5	20	155	333	16	138	267	6	185	346	3	29	55	9	94	196	54	601	1197
6	4	59	90	2	73	103	0	10	23	0	37	56	0	39	60	6	218	332
7	16	74	152	1	19	45	1	44	98	0	33	58	9	95	189	27	265	542
8	89	417	671	14	80	115	13	27	51	22	184	299	74	101	212	212	809	1348
9	13	188	261	9	149	256	1	89	121	1	166	235	6	60	103	30	652	976
10	27	144	228	10	95	152	8	187	295	2	29	42	5	50	82	52	505	799
11	1	75	128	0	40	71	1	40	84	5	69	122	1	90	150	8	314	555
12	14	111	178	2	17	30	0	135	173	1	5	7	16	75	116	33	343	504
13	4	61	71	0	10	12	1	84	98	0	2	2	0	55	63	5	212	246
14	2	18	28	0	7	11	4	32	56	1	5	6	3	28	40	10	90	141
15	2	39	64	0	75	129	3	114	190	0	48	61	2	99	142	7	375	586
16	7	49	67	3	206	253	4	72	81	1	2	3	5	84	115	20	413	519
17	11	39	52	2	5	8	0	17	19	5	13	18	22	55	89	40	129	186
18	3	58	73	3	54	75	0	86	124	0	7	10	3	29	45	9	234	327
19	45	154	228	3	60	80	3	79	97	0	2	2	10	56	79	61	351	486
20	2	25	43	0	25	41	3	172	245	5	89	131	10	181	267	20	492	727
21	7	125	248	5	110	185	0	105	185	0	15	20	5	99	177	17	454	815
22	9	146	243	4	47	92	1	70	138	1	6	8	4	84	133	19	353	614
23	0	7	18	1	12	40	0	6	19	0	0	0	1	1	6	2	26	83
24	18	107	147	43	380	514	19	173	229	0	23	27	13	90	118	93	773	1035
25	6	63	126	2	25	50	3	87	166	1	9	23	2	98	213	14	282	578
26	1	63	125	2	74	131	0	51	78	0	6	10	1	25	48	4	219	392
27	6	41	98	0	16	30	1	67	113	0	2	6	2	29	49	9	155	296
28	1	7	10	0	4	5	0	0	0	0	1	2	1	1	2	2	13	19
29	10	70	89	1	13	15	4	27	35	0	2	2	1	27	30	16	139	171
30	9	112	130	4	41	47	0	25	26	0	0	0	0	19	20	13	197	223
31	7	32	59	1	16	23	2	43	79	1	0	1	2	12	18	13	103	180
32	41	66	137	8	5	14	3	47	68	0	0	0	19	31	57	71	149	276
33	48	106	210	50	60	140	9	69	106	16	36	63	50	73	162	173	344	681
34	0	5	11	0	2	5	0	32	75	0	2	5	0	23	84	0	64	180
Total	451	2860	4863	201	2018	3292	104	2390	3845	67	900	1396	295	2003	3444	1118	10171	16840
% of deaths	9.3	58.8		6.1	61.3		2.7	62.2		4.8	64.5		8.6	58.2		6.6	60.4	

P = Partial. C = Complete. D = Death.

to the more limited choice of anesthesia for operations that are likely to have partial necropsy. For example, necropsy following craniotomy is likely to be limited to examination of the head; because halothane is by far the most common agent (57 percent) for craniotomy, the high incidence of partial necropsy for halothane is expected.

Failure to Obtain Necropsy

No necropsy was performed in 5551 deaths, only partial necropsy in 1118 deaths. These two groups represented the greatest loss of information in the study of massive hepatic necrosis. On the basis of clinical evidence, 13 of the nonnecropsied deaths were classified by the principal investigator as "probable massive hepatic necrosis" on the death abstraction form (Form III).* Of these, one was in the halothane category, three in nitrous oxide-barbiturate, five in cyclopropane, and four in Other. A review** of the death-certificate diagnoses (Form IV) and other information on Form III gave presumptive evidence of hepatic failure in an additional 241 of the nonnecropsied deaths. Of these 241 patients, 20.8 percent had received halothane, whereas the over-all use of halothane in the Study was 29.8 percent. The possibility, implied by these data, that necropsy may have been more likely to be performed in a patient with hepatic disease if he had received halothane is discussed in Chapter III-3.

Necropsy Summaries with No Mention of the Liver

Special attention was given to the possible loss of material in the 4204 necropsies whose abstracts did not mention the liver. Six institutions (1, 9, 19, 20, 22, and 27) were visited and 753 necropsy files were examined (approximately 18 percent of the 4204 cases). These institutions

*See Chapter II-2 for details of the several forms mentioned in this chapter.

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taken as an appropriate cross section of participating institutions. The microscopic description of each of these cases recorded in the yearly, permanent records of the institution's pathology department was reviewed. Without exception, the necropsy reports that were examined were in order and readily available.

Of the 753 cases reviewed, there were 28 with mention of some degree of necrosis in the necropsy protocol. Almost all necrosis appeared to be minimal, according to descriptive terminology. Three cases might have been in the intermediate group if they had been reviewed microscopically. No cases were diagnosed or described as massive hepatic necrosis. The rate of occurrence of massive necrosis in the 5967 cases in which the liver was mentioned was approximately 1.4 percent. If this rate had prevailed in the necropsies whose abstracts did not mention the liver, 59 cases of massive hepatic necrosis would have been expected in this group of necropsies. That none was found provides additional confidence in the reporting procedures of the Study and gave documentary support to the opinions of the members of the Pathology Panel, who considered it unlikely that massive hepatic necrosis could be overlooked in this group of necropsies.

The extent of confirmation and support was, of course, limited because the sample was not to be regarded as 753 of 4204 cases with no mention of the liver, which would be a large sample, but rather as six of 34 hospitals. If one hospital of the 34 had missed cases of massive hepatic necrosis, the chance was 0.82 that the sample of six hospitals visited would not include that hospital. If two hospitals had missed cases, the chance was 0.67 that the sample would not include either. For three hospitals, the chance was 0.55; for four, it was 0.44; and for ten, it was 0.10. Thus, it would have been easy for a sample of six not to include any of a small number of hospitals that had missed cases. If such a hospital existed among the 34, it could readily have missed several cases. The weakness of the evidence supplied by the small sample emphasizes the importance of the opinions of the pathologists in reaching a conclusion as to the chances of overlooking massive hepatic necrosis.

Finding three cases in the six hospitals that might have fallen into the intermediate necrosis group was not surprising, inasmuch as the protocol was designed to retrieve only massive hepatic necrosis. The opinions of the pathologists and the results of the sampling suggest that the probability of massive hepatic necrosis among the cases whose necropsies did not mention the liver was small.

MASSIVE HEPATIC NECROSIS

Identification of Cases of Massive Hepatic Necrosis

Possible cases of massive hepatic necrosis were collected for pathology review by the series of steps outlined in Chapter II-2 and schematized in Fig. 2.

Fewer than half the finally verified cases of massive hepatic necrosis (31 of 82) were elicited by the initial request for all cases of massive hepatic necrosis (Table 3). Prescreening for necrosis by the principal investigators introduced a bias not originally recognized and therefore not anticipated in the original protocol. The investigators' knowledge of the severity of the surgical procedure seemed to constitute the largest biasing factor, but knowledge of the anesthetic agent may also have contributed to this bias. Fortunately, bias was recognized soon enough to allow additions to the multistage review of necropsy reports, which ensured collection of slides of even remotely suspicious cases.

The small number of verified cases of massive hepatic necrosis accrued from the relatively large number of possible cases submitted also reflects difficulties in nomenclature and diagnosis (discussed in Chapter III-2).

In examining the liver, each Panel member substantiated the existence of necrosis and indicated its degree. The degree of necrosis was arbitrarily classified as: 1+, not more than 25 percent of the lobular parenchyma affected; 2+, between 25 and 50 percent of the parenchyma affected; 3+, approximately 75 percent of the parenchyma destroyed; or 4+, almost all or all the parenchyma destroyed. For each case, the necrosis ratings of all five pathologists were averaged, and the cases were separated into three categories: massive necrosis, average score 2.6 or greater; intermediate, 1.5 to 2.5; and minimal, 0 to 1.4.

There were 82 cases of massive hepatic necrosis out of 10,171 necropsies, or approximately one in 125 necropsies and approximately one in 10,000 administrations of general anesthesia. There were 115 cases of intermediate hepatic necrosis and 25 cases of minimal necrosis collected as a byproduct of the search for massive necrosis cases. These accrued because of the leniency in interpretation of degree of necrosis prescribed to the "local selector" and the pathologist who reviewed the 4204 necropsy summaries. Because the intent of the protocol and its addenda was not to collect cases of intermediate and minimal necrosis (and there is no assurance that all were collected), these cases are generally excluded from the comparisons that follow.*

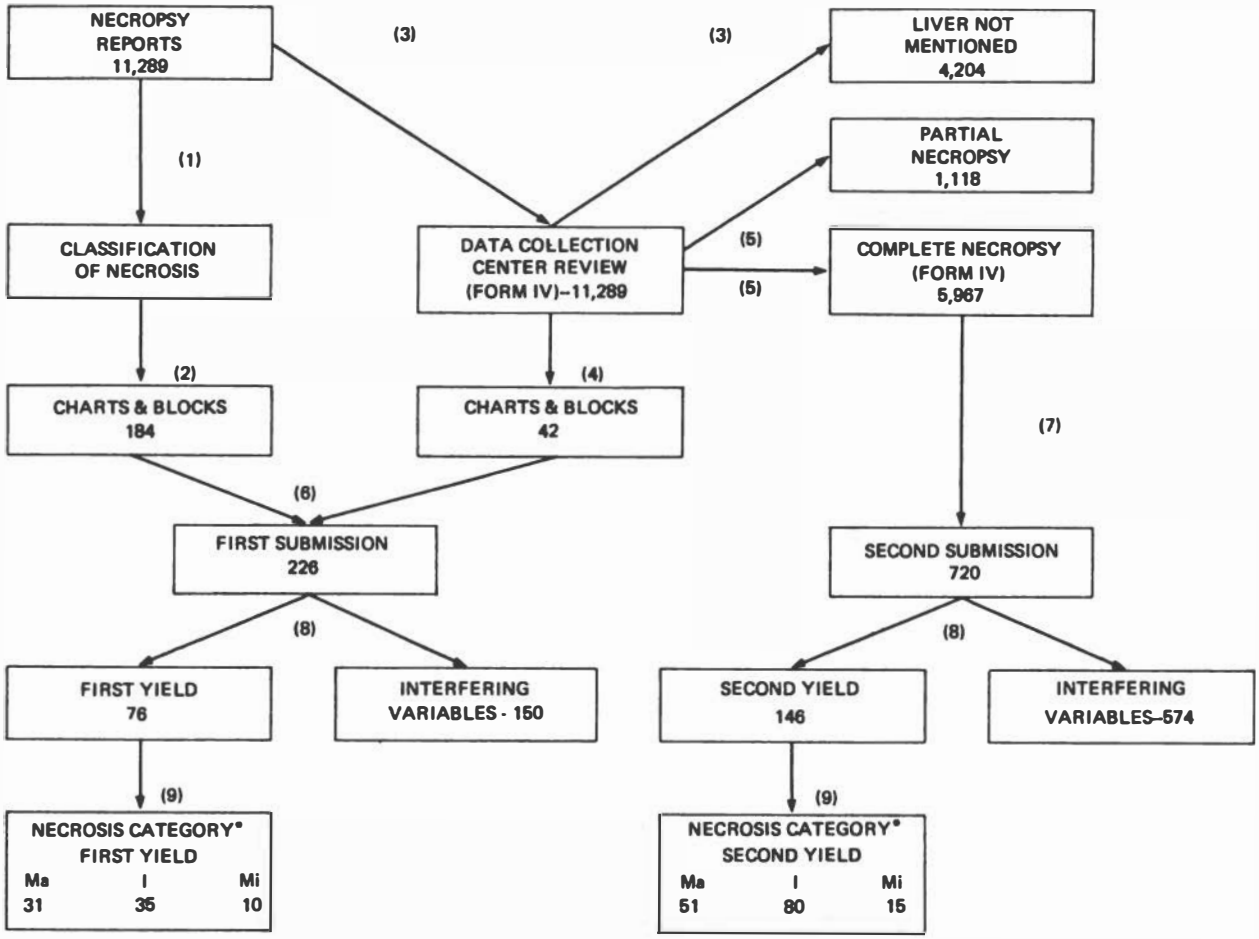
Massive Hepatic Necrosis in Relation to Anesthetic Practice

Observed occurrences of massive necrosis after all operations (Table 4) for the five anesthetic practices ranged from 5.9 below the expected (nitrous oxide-barbiturate) to 10.9 above

*Data from the two-way comparisons presented in this section cannot be fully interpreted unless multiple adjustments are made simultaneously. The small number of cases of massive hepatic necrosis precludes this type of analysis.

FIGURE 2

SCHEMATIC FOR PATHOLOGY DATA FLOW



LEGEND:

Step 1	Necropsy reports classified by principal investigator or designate.
Step 2	For cases thought to be massive hepatic necrosis, complete charts were sent to Data Collection Center. Slides or blocks of liver were sent to AFIP, Washington, D.C.
Step 3	Necropsy summary (Form IV) for all necropsy reports completed by principal investigator.
Step 4	Hepatitis and possible necrosis charts and slides or blocks requested.
Step 5	Form IV categorized at Data Collection Center.
Step 6	Slides prepared for circulation, charts abstracted.
Step 7	Form IV summaries reviewed by consultant pathologist. Slides requested from participating institutions on the basis of the above review.
Step 8	Submissions screened for interfering variables by consultant pathologist.
Step 9	Necrosis and other morphologic variables rated by Pathology Panel.

*Necrosis Category: Ma = Massive, I = Intermediate, Mi = Minimal

TABLE 3.--PATHOLOGY PANEL RATINGS OF HEPATIC NECROSIS BASED ONLY ON SLIDES

	Hal	N-B	Cyclo	Ether	Other	Total
Massive necrosis	26 (13)*	15 (3)	25 (9)	5 (1)	11 (5)	82 (31)
Intermediate necrosis	48 (13)	19 (4)	24 (14)	8 (2)	16 (2)	115 (35)
Minimal necrosis	6 (3)	8 (2)	3 (1)	3 (2)	5 (2)	25 (10)
TOTAL	80 (29)	42 (9)	52 (24)	16 (5)	32 (9)	222 (76)

*Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

TABLE 4.--OBSERVED AND EXPECTED OCCURRENCE OF MASSIVE HEPATIC NECROSIS FOLLOWING HIGH-, MIDDLE-, AND LOW-DEATH-RATE OPERATIONS

Operation	Group	Hal	N-B	Cyclo	Ether	Other	Total
Low-death-rate operations	Necrosis observed	2	0	1	0	0	3
	Necrosis expected*	0.7	0.9	0.6	0.4	0.5	3
	EA** (in thousands)	86.7	105.3	67.5	50.1	57.4	367.0
	Number of deaths	234	209	175	63	163	844
	Rates/10,000 EA	0.23	0	0.15	0	0	0.08
	Rates/1,000 deaths	8.55	0	5.71	0	0	3.55
Middle-death-rate operations	Necrosis observed	13	6	17	4	7	47
	Necrosis expected	16.1	11.1	7.5	4.9	7.4	47
	EA (in thousands)	146.2	101.3	68.1	44.3	67.5	427.4
	Number of deaths	2562	1757	2397	837	2073	9626
	Rates/10,000 EA	0.89	0.59	2.50	0.90	1.04	1.10
	Rates/1,000 deaths	5.07	3.41	7.09	4.78	3.38	4.88
High-death-rate operations	Necrosis observed	11	9	7	1	4	32
	Necrosis expected	11.3	6.0	6.1	3.9	4.7	32
	EA (in thousands)	21.8	11.6	11.7	7.6	9.1	61.7
	Number of deaths	2066	1323	1270	492	1205	6356
	Rates/10,000 EA	5.05	7.78	5.99	1.31	4.40	5.18
	Rates/1,000 deaths	5.32	6.80	5.51	2.03	3.32	5.03
Operations unknown	EA (in thousands)	0.2	0.1	0	0	0.1	0.4
	Number of deaths	1	3	3	4	3	14
All operations	Necrosis observed	26	15	25	5	11	82
	Necrosis expected	24.4	20.9	14.1	9.8	12.8	82
	EA (in thousands)	254.9	218.2	147.4	102.0	134.0	856.5
	Number of deaths	4863	3292	3845	1396	3444	16840
	Number of complete necropsies	2860	2018	2390	900	2003	10171
	Rates/10,000 EA	1.02	0.69	1.70	0.49	0.82	0.96
	Rates/1,000 deaths	5.35	4.56	6.50	3.58	3.19	4.87
	Rates/1,000 necropsies	9.1	7.4	10.5	5.6	5.5	8.1

LEGEND: The numbers of necroses expected were computed by distributing the observed necrosis cases proportional to the number of estimated administrations. For example:

$$\text{*Necrosis expected (Hal)} = \frac{\text{total necrosis X estimated administrations (Hal)}}{\text{total estimated administrations}}$$

$$= \frac{3 \times 86.7}{367.0}$$

$$= 0.7$$

**Estimated administrations.

the expected (cyclopropane). (The number of necroses expected was calculated by means of the formula given in the legend of Table 4.) Of the five anesthetic practices, cyclopropane and halothane were associated with the highest massive hepatic necrosis rates per 1000 necropsies: 10.5 and 9.1, respectively.

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

TABLE 5.--OBSERVED AND EXPECTED OCCURRENCE OF MASSIVE HEPATIC NECROSIS FOLLOWING SINGLE PROCEDURES

	Hal	N-B	Cyclo	Ether	Other	Total
Necrosis observed	13	13	21	5	5	57
Necrosis expected	16.8	15.3	9.9	6.9	8.3	57
EA (in thousands)	228.6	207.4	134.6	93.6	110.7	775.1
Number of deaths	3859	2822	2924	1135	2424	13164
Number of necropsies*	2595	1892	1890	785	1595	8757
Rates/10,000 EA**	0.6	0.6	1.5	0.5	0.5	0.7
Rates/1000 deaths	3.4	4.6	7.2	4.4	2.1	4.4
Rates/1000 necropsies	5.0	6.9	11.1	6.4	3.1	6.5

*Complete and incomplete. **Estimated administrations.

were open-heart operations, exploratory laparotomy, and large-bowel procedures. All other operations were arbitrarily categorized in the middle-death-rate group.

Massive hepatic necrosis occurred more frequently after operations associated with high death rates: there were three cases of massive necrosis after 366,992 low-death-rate operations (or approximately 0.1 per 10,000); 47 after 427,355 middle-death-rate operations (1.1 per 10,000); and 32 after 61,719 high-death-rate operations (five per 10,000).

The rates of massive hepatic necrosis after single procedures within 6 weeks of death are shown in Table 5. The occurrence ranged from 11.1 above the expected (cyclopropane) to 3.8 below the expected (halothane). Cyclopropane is high with a massive hepatic necrosis rate of 11.1 per 1000 necropsies.

Massive Hepatic Necrosis in Relation to Type of Operation

Massive hepatic necrosis occurred most frequently after open-heart surgery (Table 6). Nearly one-fourth (19) followed open-heart operations with cardiopulmonary bypass, although these procedures accounted for only 1 percent of all operations in the Study. That massive hepatic necrosis following open-heart operations appeared predominantly in the second yield,* i.e., were not submitted by local selector, supports the inference that there were screening biases at the local institutions. Thus, easily explained or seemingly easily explained necrosis (such as that following open-heart surgery) was rejected initially but collected later as part of the second yield.

Operations on the large blood vessels (primarily the aorta), on the stomach, and for 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 relatively high incidences of massive necrosis (nine, eight, and nine cases, respectively).

Contrary to expectations, an increased incidence of massive hepatic necrosis following biliary tract operations did not occur. An estimated 27,677 patients underwent cholecystectomy with or without common-duct exploration and other major surgery. Massive hepatic necrosis occurred in only six of these, a rate somewhat less than that for most other abdominal operations. One of the six patients had received halothane, whereas halothane was administered for approximately 30 percent of the cholecystectomies with or without common-duct exploration. Massive hepatic necrosis occurred in an additional three patients who had undergone a biliary tract procedure at a previous operation within 6 weeks of death, and one of these had received halothane.

Massive Hepatic Necrosis in Relation to Multiple Administrations of Anesthesia

There were 25 massive hepatic necroses in the 81,400 patients who had two or more operations that qualified them for the multiple procedure category.** Table 7 shows that the incidence of massive hepatic necrosis was considerably higher in patients who had undergone multiple procedures (25 of 81,400 or 3.1 per 10,000) than in patients who had not (57 of 775,100 or 0.7 per 10,000, as shown in Table 5). Those who received halothane for at least two procedures had higher rates than expected (10 cases, rather than 4.3); those who had cyclopropane for the last procedure had the expected rates; and those who had nitrous oxide-barbiturate, ether, or Other for the last procedure had lower than the expected rates. The 25 patients in the multiple procedure category underwent 27 types of operations. Of these 27, 14 were abdominal and represent 13 deaths. No other region*** contributed more than three deaths. It

*See Fig. 2 for definition of first and second yields.

**To qualify for this category, it was arbitrarily agreed that two or more operations should occur within 6 weeks. The selection of patients to meet this criterion was approximate, and included patients who had at least two operations under general anesthesia in the same month if the last operation was done after the 15th of that month, or two operations in the same month or consecutive months if the last operation was done on or before the 15th day of the month.

***"Regions" were the abdomen, chest, extremities, head, neck, soft tissue, and genitourinary tract.

TABLE 6.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY OPERATION AND ANESTHETIC PRACTICE

Operation or Region	Halothane		N-B		Cyclo		Ether		Other		Total		Rates/ 10,000 EA
	EA*	MHN**	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
Mouth					6.0	1					80.2	1	0.13
Craniotomy	9.4	3(2)***									16.8	3 (2)	1.8
Endoscopy	5.0	1 (1)									15.7	1 (1)	0.82
Lung	4.4	1 (1)	2.2	2	1.1	1					10.0	4 (1)	4.0
Heart-pump	3.8	6	2.3	9 (1)	0.8	1	0	1 (1)	1.7	2	8.7	19 (2)	21.8
Heart	3.2	1									7.9	1	1.3
Mediastinum					0.3	1			0.7	1	4.2	2	4.76
Cholecystectomy	4.0	1 (1)			4.2	1 (1)					13.8	2 (2)	1.45
Cholecystectomy & bile duct					1.5	2					6.3	2	3.2
Cholecystectomy & other			1.3	2 (1)							7.6	2 (1)	2.6
Subphrenic abscess	0.02	1 (1)									.2	1 (1)	50
Expl. lap.	4.2	2 (1)			5.5	5 (4)			3.3	2 (2)	18.4	9 (7)	4.9
Stomach	3.1	2 (1)			4.8	3 (1)	3.6	1	2.7	2 (1)	16.1	8 (3)	5.0
Small bowel					0.2	2 (1)	0.03	1	0.2	1 (1)	5.4	4 (2)	7.4
Large bowel					1.9	1					17.9	1	0.56
Evisceration	0.3	1 (1)									1.2	1 (1)	0.83
Vessel graft			1.1	2 (1)	1.5	4 (1)			0.09	3 (1)	7.2	9 (3)	12.5
Symp., adren.	1.0	1									3.2	1	3.1
Spleen, liver	0.6	2 (1)			1.1	1	0.3	1			3.1	4 (1)	7.4
Cesarean					1.4	1 (1)					2.5	1 (1)	4.0
Male genito-urinary	2.8	1									11.6	1	0.86
Bone closed					0.9	1					9.5	1	1.05
Soft tissue	7.1	1 (1)									16.8	1 (1)	0.60
Femur open							0	1			10.4	1	0.96
Plastic	14.0	2 (2)									40.4	2 (2)	0.49
All others	--	--	--	--	--	--	--	--	--	--	521.4	--	--
TOTALS	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Massive hepatic necrosis.
***Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).
Note: Columns and rows need not total for EA because entries are made only if MHN occurred in a given category.

TABLE 7.--OBSERVED AND EXPECTED OCCURRENCES OF MASSIVE HEPATIC NECROSIS FOLLOWING MULTIPLE PROCEDURES

	Hal on previous operations		No Hal on previous operations		Total
	Hal last op.	No Hal last op.	Hal last op.	No Hal last op.	
Necrosis observed	10	0	3	12	25
Necrosis expected	4.3	2.8	3.7	14.1	25
EA (in thousands)	14.1	9.1	12.2	46.0	81.4
Number of deaths	480	455	524	2217	3676
Number of necropsies	352	312	364	1504	2532
	N-B last op.	No N-B last op.	N-B last op.	No N-B last op.	Total
Necrosis observed	0	10	2	13	25
Necrosis expected	0.5	6.6	2.8	15.1	25
EA (in thousands)	1.6	21.6	9.0	49.2	81.4
Number of deaths	74	861	396	2345	3676
Number of necropsies	51	613	276	1592	2532
	Cyclo last op.	No Cyclo last op.	Cyclo last op.	No Cyclo last op.	Total
Necrosis observed	0	10	4	11	25
Necrosis expected	0.6	6.6	3.4	14.5	25
EA (in thousands)	1.8	21.4	11.0	47.2	81.4
Number of deaths	150	785	771	1970	3676
Number of necropsies	100	564	504	1364	2532
	Ether last op.	No Ether last op.	Ether last op.	No Ether last op.	Total
Necrosis observed	0	10	0	15	25
Necrosis expected	0.3	6.8	2.3	15.5	25
EA (in thousands)	0.9	22.3	7.6	50.6	81.4
Number of deaths	19	916	242	2499	3676
Number of necropsies	9	655	173	1695	2532
	Other last op.	No Other last op.	Other last op.	No Other last op.	Total
Necrosis observed	0	10	6	9	25
Necrosis expected	1.5	5.6	5.7	12.2	25
EA (in thousands)	4.9	18.3	18.4	39.8	81.4
Number of deaths	212	723	808	1933	3676
Number of necropsies	152	512	551	1317	2532

is striking that none of these 25 patients was jaundiced before the last administration of anesthesia (Table 8). Two patients had pre-existing hepatic disease and 11 developed jaundice after the final anesthetic and before death. All but one died within 11 days of operation.

Incidence of Massive Hepatic Necrosis for Each Institution

Table 9 displays the rate of massive hepatic necrosis for each institution. Eleven institutions had no massive hepatic necrosis (3, 7, 13, 14, 23, 26, 27, 28, 31, 32, and 34). They contributed 191,400 cases to the 856,500 studied. Seven institutions had five or more necrosis cases (8, 10, 20, 21, 22, 24, and 30) and contributed very heavily (283,900) to the total cases in the Study. Two institutions, 24 and 30, stand out as having high massive necrosis rates (6.5 and 12.5 per 10,000 administrations, respectively). These institutions also had large numbers of operations associated with high rates of massive hepatic necrosis* and high death rates. These factors undoubtedly contributed to the high rates of massive hepatic necrosis in the two institutions.

*Four operation categories had notably higher rates of massive hepatic necrosis than all others: heart with pump, laparotomy, stomach, and great vessels.

TABLE 8.--SUMMARY OF MASSIVE HEPATIC NECROSIS CASES WITH MULTIPLE PROCEDURES

Case	Age	Sex	Anesthetic practice prev. ops.	Anesthetic practice last op.	Alcoholism	Pre-exist. hepatic disease	Jaundiced before death	Jaundiced before last op.	Day of death after last op.
1	67	M	Hal	Hal	Unknown	No	Yes	No	3
36	25	M	Hal	Hal	Unknown	No	Yes	No	5
44	64	M	Hal	Hal	Yes	No	Yes	No	3
55	72	M	No Hal	Other	Unknown	No	No	No	2
68	42	M	No Hal	Other	Unknown	No	Yes	No	1
91	66	F	Hal	Hal	Unknown	No	Yes	No	8
93	63	M	No Hal	Cyclo	Unknown	No	No	No	3
97	67	M	Hal	Hal	Yes	No	Yes	No	9
99	21	M	Hal	Hal	Unknown	No	No	No	5
100	39	M	Hal	Hal	Unknown	No	Yes	No	10
122	58	F	Hal	Hal	Unknown	No	Yes	No	5
156	41	M	No Hal	Cyclo	Unknown	Unknown	Unknown	No	2
185	57	M	No Hal	Hal	Unknown	Yes	Yes	No	1
345	34	M	No Hal	Hal	Yes	No	Yes	No	7
616	81	M	No Hal	Other	Unknown	Yes	No	No	3
636	55	M	Hal	Hal	Unknown	No	No	No	3
649	65	M	No Hal	Other	Yes	No	No	No	3
675	80	F	No Hal	Cyclo	Unknown	No	No	No	27
687	48	M	No Hal	N-B	Unknown	No	Yes	No	4
691	64	M	Hal	Hal	Unknown	No	No	No	11
707	21	M	No Hal	Other	Unknown	No	No	No	3
709	37	F	No Hal	N-B	Unknown	Unknown	No	No	2
711	33	M	No Hal	Hal	Unknown	No	No	No	7
717	66	M	No Hal	Other	Unknown	No	No	No	2
719	62	F	No Hal	Cyclo	Unknown	No	No	No	8

TABLE 9.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY INSTITUTION AND ANESTHETIC PRACTICE

Institution	Halothane		N-B		Cyclo		Ether		Other		Total		Rate of MHN/ 10,000 EA
	EA*	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
1	16.6	2(2)**									39.9	2 (2)	0.5
2					1.9	2 (1)					9.5	2 (1)	2.1
3												0	
4					3.5	3					29.2	3	1.0
5					15.8	3 (2)					32.9	3 (2)	0.91
6									7.2	1 (1)	30.3	1 (1)	0.33
7												0	
8	36.3	3 (2)	16.0	1	1.4	1	25.5	1	11.9	2	91.2	8 (2)	0.88
9	7.3	2 (2)	19.4	1	3.3	1 (1)					55.5	4 (3)	0.72
10	13.5	1 (1)	5.7	2	5.2	3 (1)	3.1	1			29.2	7 (2)	2.4
11			4.3	2 (1)	2.7	1			4.0	1	26.3	4 (1)	1.5
12	8.2	1 (1)			11.9	2 (2)					25.1	3 (3)	1.2
13												0	
14												0	
15					9.6	2	3.3	1			30.3	3	0.99
16			8.2	1 (1)							16.1	1 (1)	0.62
17									5.5	2 (2)	19.8	2 (2)	1.0
18					2.4	1 (1)					8.9	1 (1)	1.1
19	7.2	1 (1)									18.3	1 (1)	0.55
20	3.0	1			21.8	2 (1)	7.0	1 (1)	10.7	1 (1)	47.5	5 (3)	1.1
21	22.4	2	15.1	3 (1)	12.7	1			13.4	1 (1)	65.1	7 (2)	1.1
22	14.1	4 (1)	3.8	2							31.2	6 (1)	1.9
23												0	
24	2.5	3 (1)	11.2	3	0.9	1	0.2	1	0.6	2	15.3	10 (1)	6.5
25									2.1	1	8.4	1	1.2
26												0	
27												0	
28												0	
29	2.5	2 (1)									3.9	2 (1)	5.1
30	2.3	3			0.3	2					4.4	5	12.5
31												0	
32												0	
33	5.7	1 (1)									26.8	1 (1)	0.38
34												0	
TOTALS	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).
Note: Columns and rows need not total for EA because entries are made only if MHN occurred in a given category.

Massive Hepatic Necrosis in Relation to Preoperative Physical Status

Preoperative "physical status" is frequently not entered on the anesthesia record. Nine of the 82 cases of massive hepatic necrosis occurred in patients whose physical status had not been assigned preoperatively. In addition to the nonassignment problem (discussed in Chapter II-2), the designation of physical status varies considerably among institutions and anesthesiologists, because the criteria are so general. As an example of the unreliability of this classification, Table 10 lists five patients who suffered massive hepatic necrosis and who were evaluated preoperatively as physical status 1, i.e., "no complicating systemic disturbance." Of the five patients, three had severe debilitating disease for which they were to undergo definitive surgery, the fourth was 70 years old and had arteriosclerotic heart disease, and the fifth had a recent history of perforated duodenal ulcer. Clearly, none of these cases should have been classified as physical status 1.

In spite of the serious limitation imposed by inaccurate or absent assignment of physical status, there was a clear pattern of increasing massive hepatic necrosis rates for patients in poorer preoperative physical status (Table 11). For nonemergency cases, the rates of massive hepatic necrosis for "good-risk" patients (physical status 1 and 2) were 0.12 and 0.84 per 10,000 administrations, whereas the rates for "poor-risk" patients (physical status 3 and 4) were 3.6 and 12.7 per 10,000. A similar pattern was observed for emergency operations, and patients listed preoperatively as "moribund" (physical status 7) had the highest rate of massive hepatic necrosis, 22.6 per 10,000 estimated administrations.

Incidence of Massive Hepatic Necrosis for Each Year of the Study

There was an increase in over-all incidence of massive hepatic necrosis during the period of study, from 15 cases in 1959 to 24 in 1962 (Table 12). At the same time, the use of halothane increased markedly, from 13 percent in 1959 to 50 percent in 1962. Many suspected that the increase in total incidence of necrosis might be caused by the increased use of halothane. The data failed to support this possibility, because, although the number of cases of massive hepatic necrosis following halothane increased during the 4-year period, this increase was roughly in proportion to the increase in over-all use of halothane. In fact, the rates of massive hepatic necrosis following halothane and following all agents combined were approximately the same for the 4 years individually, as well as combined. By contrast, the incidence of massive hepatic necrosis following cyclopropane remained approximately the same, but the rate was rising because the over-all use of cyclopropane dropped by 25 percent from 1959 to 1962. The absence of massive hepatic necrosis following nitrous oxide-barbiturate in 1962 is puzzling.

No good alternate explanation for the increase in massive hepatic necrosis during the 4-year period is apparent from the data. It seemed likely that the number of difficult operations, such as open-heart procedures, which are followed more frequently by hepatic necrosis, might be increasing, but that proved not to be the case (Table 13). In the absence of any better explanation, it is reasonable to assume that the increase in postoperative necrosis observed in this Study may simply reflect the over-all increase in viral and other forms of hepatitis that have been reported for recent years.

Massive Hepatic Necrosis in Relation to Other Variables

Age

Massive hepatic necrosis occurred in all age groups (Table 14), but the rates were lowest in the youngest (0 to 9 years) group and highest in the oldest (80 to 89 years) group.

Sex

Tabulation of the incidence of massive necrosis by sex (Table 14) shows a ratio of 51 males to 31 females; and the rate of necrosis for males was twice that for females. However, the over-all death rate for males was 2.56 and for females it was 1.44; thus the necrosis rates parallel the death rates, and the rates calculated on the basis of estimated administrations are misleading.

Duration of Anesthesia

The rate of massive hepatic necrosis increased with the duration of anesthesia (Table 15). These rates varied from 0.28/10,000 estimated administrations for procedures lasting under ½ hr to 10.5/10,000 estimated administrations for procedures lasting over 6½ hr. The type of operation and preoperative physical status probably contributed more heavily to these rates than the duration of anesthesia. This assumption is based on the fact that multiple adjustments tended to minimize the effect of duration of anesthesia on death rates.

Day of Death

Necrosis by day of death is shown in Table 16. There were 54 deaths in the massive necrosis group within 1 week of surgery; this represents about 66 percent of all massive necrosis deaths.

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

TABLE 10.--CASES OF MASSIVE HEPATIC NECROSIS CLASSIFIED AS PHYSICAL STATUS 1

Age, years	Preoperative diagnosis	Comment
67	Cancer esophagus	Ulcerating lesion lower third esophagus
49	Duodenal ulcer	Had perforated ulcer with surgery 6 weeks before
70	Elective cholecystectomy	Arteriosclerotic heart disease
13	Atrial septal defect	
13	I.V. septal defect, patent ductus	Cyanotic on admission

TABLE 11.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY PHYSICAL STATUS AND ANESTHETIC PRACTICE

Physical status	Halothane		N-B		Cyclo		Ether		Other		Total		Rate/ 10,000 EA
	EA*	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
1	121.9	3 (2)**	109.9	1					65.0	1 (1)	421.7	5 (3)	0.12
2	60.2	7 (5)	48.8	4 (1)	27.3	3 (1)	20.1	1			184.0	15 (7)	0.84
3	15.9	4 (1)	12.5	3	7.0	7 (1)	5.7	2 (1)	9.1	2	50.2	18 (3)	3.6
4	2.3	5 (1)	1.3	3 (1)							6.3	8 (2)	12.7
5					14.1	3 (3)					38.2	3 (3)	0.79
6	4.2	4 (2)	3.4	1 (1)	6.2	8 (2)			3.3	4 (2)	18.2	17 (7)	9.3
7	0.7	1	0.5	1	1.1	3 (2)			0.7	2 (1)	3.1	7 (3)	22.6
Not recorded	39.4	2 (2)	34.6	2	22.5	1	15.7	2	22.6	2 (1)	134.8	9 (3)	
TOTALS	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

TABLE 12.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY YEAR AND ANESTHETIC PRACTICE

Year	Halothane		N-B		Cyclo		Ether		Other		Total		Rates/ 10,000 EA
	EA*	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
1959.....	22.8	2 (1)**	73.6	4	42.6	6 (3)	35.9	2 (1)	32.5	1 (1)	207.3	15 (6)	0.72
1960.....	48.0	6 (3)	60.0	4 (2)	39.8	6 (1)	30.3	1	33.3	2	211.4	19 (6)	0.90
1961.....	74.0	5 (3)	49.4	7 (1)	34.5	7 (2)	20.2	1	32.7	4 (1)	210.7	24 (7)	1.14
1962.....	110.2	13 (6)	35.2	0	30.5	6 (3)	15.7	1	35.5	4 (3)	227.1	24 (12)	1.06
TOTALS.....	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

TABLE 13.--ANNUAL INCIDENCE OF OPERATIONS WITH HIGH MASSIVE HEPATIC NECROSIS*

	Year			
	1959	1960	1961	1962
Estimated administrations	11,500	13,400	12,100	12,300

*Heart with pump, laparotomy, stomach, great vessels.

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TABLE 14.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY SEX AND ANESTHETIC PRACTICE

Sex	Halothane		N-B		Cyclo		Ether		Other		Total		Rates/ 10,000 EA
	EA*	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
Male.....	120.6	17 (8)**	83.2	7 (2)	49.6	14 (5)	50.3	4 (1)	65.7	9 (4)	369.4	51 (20)	1.38
Female.....	134.3	9 (5)	135.0	8 (1)	97.8	11 (4)	51.7	1	68.3	2 (1)	487.1	31 (11)	0.64
TOTALS.....	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY AGE GROUP AND ANESTHETIC PRACTICE

Age	Halothane		N-B		Cyclo		Ether		Other		Total		Rates/ 10,000 EA
	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
0 - 9.....					13.7	1	35.4	1	45.5	1	137.1	3	0.22
10 - 19.....	26.6	3 (1)	19.0	5 (1)					10.6	1	75.8	9 (2)	1.2
20 - 29.....	27.0	3 (2)	31.9	3 (1)	23.0	1 (1)			9.5	1	98.7	8 (4)	0.82
30 - 39.....	36.8	5 (2)	38.8	2	26.6	1 (1)					126.2	8 (3)	0.64
40 - 49.....	42.2	1 (1)	41.6	1	27.2	3 (1)	12.0	2 (1)	16.1	3 (3)	139.1	10 (6)	0.72
50 - 59.....	37.7	5 (2)	34.4	3 (1)	19.8	8 (4)			15.7	1 (1)	119.1	17 (8)	1.4
60 - 69.....	32.4	7 (4)	28.9	1	16.5	7 (1)			13.1	2	100.9	17 (5)	1.7
70 - 79.....	13.0	1 (1)			7.9	3 (1)	4.9	1	7.7	1 (1)	47.0	6 (3)	1.3
80 - 89.....	2.5	1			2.3	1	1.0	1	1.9	1	11.4	4	3.5
TOTALS.....	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).
Note: Columns and rows need not total for EA because entries are made only if MHN occurred in a given category.

TABLE 15.--INCIDENCE AND RATES OF MASSIVE HEPATIC NECROSIS BY DURATION OF ANESTHESIA AND ANESTHETIC PRACTICE

Length of anesthesia	Halothane		N-B		Cyclo		Ether		Other		Total		Rate/ 10,000 EA
	EA*	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	EA	MHN	
0 - 1/2 hr.....	23.0	2 (2)**			20.8	1 (1)					108.2	3 (3)	0.28
1/2 - 1 hr.....	55.0	2 (1)			34.7	3 (1)					209.7	5 (2)	0.24
1 - 2 hr.....	79.4	4 (3)	53.1	1	44.1	8 (3)	33.2	2	38.7	3 (2)	248.5	18 (8)	0.73
2 - 4 hr.....	71.2	11 (5)	41.8	6 (1)	38.1	8 (3)			33.0	5 (2)	213.5	30 (11)	1.41
4 - 6 1/2 hr.....	20.6	3 (2)	15.0	2	8.2	4 (1)	7.7	1	10.0	3 (1)	61.7	13 (4)	2.10
Over 6 1/2 hr.....	4.8	4	3.3	6 (2)	1.2	1	1.2	2 (1)			12.4	13 (3)	10.5
TOTALS.....	254.9	26 (13)	218.2	15 (3)	147.4	25 (9)	102.0	5 (1)	134.0	11 (5)	856.5	82 (31)	0.96

*In thousands.
**Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

Note: Columns and rows need not total for EA because (1) entries are only made if massive hepatic necrosis occurred in that category, and (2) there were some cases in each common practice in which length of anesthesia was not recorded.

Five died on the day of surgery and half of the massive hepatic necrosis deaths occurred before day 4. Except for the ether category, in which there were so few deaths, the pattern of day of death for the common anesthetic practices is very similar.

Occurrence of Jaundice Before Death

Jaundice was not observed in all patients who died of massive hepatic necrosis (Table 17). The clinical pathologic implications of this are discussed in Chapter III-4. Of the 26 patients in the halothane group who died from massive hepatic necrosis, 16 were jaundiced, whereas jaundice was recorded for only 15 of the 56 who had not received halothane. Possible explanations for this considerable excess in clinical jaundice in the halothane cases of massive hepatic necrosis include the following: (1) jaundice occurs as a late manifestation of massive hepatic necrosis more frequently after halothane than after other agents; (2) jaundice occurs equally for all agents, so many patients who had massive hepatic necrosis and received agents other than halothane were not necropsied; and (3) the physician was more

TABLE 16.--INCIDENCE OF MASSIVE HEPATIC NECROSIS BY POSTOPERATIVE DAY OF DEATH AND ANESTHETIC PRACTICE

Day of death	Halothane	N-B	Cyclo	Ether	Other	Total
0		1	4			5
1	4 (1)*	2	1 (1)		2 (1)	9 (3)
2	4	2	6 (3)	1	2 (1)	15 (4)
3	5 (2)	1	2 (1)		4 (1)	12 (4)
4	1	3	1 (1)			5 (1)
5	3 (3)	1		1 (1)		5 (4)
6			1			1
7	1 (1)			1		2 (1)
8	1 (1)	2 (1)	3 (1)		1 (1)	7 (4)
9	1 (1)	1 (1)	2 (1)			4 (3)
10	1 (1)			1		2 (1)
11	1	1 (1)			1 (1)	3 (2)
14	1 (1)		1			2 (1)
15		1				1
17			1			1
19			1			1
20	1 (1)					1 (1)
22			1 (1)			1 (1)
25				1	1	2
27			1			1
35	1 (1)					1 (1)
42	1					1
TOTALS	26 (13)	15 (3)	25 (9)	5 (1)	11 (5)	82 (31)

*Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

TABLE 17.--JAUNDICE BEFORE DEATH IN CASES OF MASSIVE HEPATIC NECROSIS

	Hal	N-B	Cyclo	Ether	Other	Total
Jaundice before death	16 (11)*	4 (2)	9 (5)	1 (1)	1 (1)	31
No jaundice before death	10 (2)	11 (1)	16 (4)	4 (0)	10 (4)	51

*Numbers in parentheses are numbers of cases originally selected by principal investigators (first yield).

likely to look for, and record or measure, jaundice in terminal patients with hepatic failure if those patients had received halothane. The data do not show any basis for discriminating among these possibilities, whose statistical implications are similar to those discussed in Chapter III-3.

ETIOLOGY OF NECROSIS

Pathology Panel Review

After the members of the Pathology Panel reviewed the histologic sections from the cases culled by the local selectors, they were given clinical abstracts* that contained details of the clinical cases (knowledge of the anesthetic was withheld). Using this information and their knowledge of the histologic features, they stipulated the etiology of hepatic necrosis and placed the cases into one or more of the following categories: (1) halothane, (2) any hepatotoxin, (3) drug sensitization, (4) viral hepatitis, (5) shock, (6) anoxemia or sepsis, and (7) autolysis, etc. The pathologists worked independently and used their own criteria to determine the proper category. After the data had been reviewed, items 2, 3, 4, 5, and 6 were found suitable for survey and were grouped for convenience into the three categories shown in Table 18.

Thirty abstracts** of massive hepatic necrosis were available for review (Table 18). Five cases (64, 98, 99, 100, and 328) were considered by at least three of the five panelists who completed the review to be consistent with drug-induced hepatic injury, and five (64, 91, 122, 205, and 255) to be consistent with viral hepatitis. Four cases in each group involved halothane; only one (64) appeared in both groups.

Twenty-three cases were considered by at least three of the five panelists to be consistent with the effects of shock, anoxemia, or sepsis. Of these, seven involved halothane, three nitrous oxide-barbiturate, eight cyclopropane, one ether, and four Other. Of the 23 cases, two of the halothane cases (98 and 100) appeared in the drug injury category as well, and one of the nitrous oxide-barbiturate cases (205) appeared in the viral hepatitis category.

It is worth noting (1) that, although the Pathology Panel was allowed to enter a given case in more than one category, only four cases (64, 98, 100, and 205) consistently appeared in more than one category; and (2) that there was more conformity of scoring in the category of shock, anoxemia, or sepsis.

**One chart submitted too late for Panel review (345).

TABLE 18.--ETIOLOGY OF MASSIVE HEPATIC NECROSIS ASSESSED BY PATHOLOGY PANEL

Case	Anesthetic practice	Number of pathologists scoring*		
		Consistent with drug-induced hepatic injury	Consistent with effects of shock, anoxemia, or sepsis	Consistent with effects of viral hepatitis
1	Hal	2	5	0
36	Hal	2	5	0
44	Hal	2	4	1
51	Other	2	2	2
55	Other	1	5	0
64	Hal	3	1	3
68	Other	1	5	0
72	Cyclo	0	5	1
74	Cyclo	2	4	1
81	Cyclo	2	3	2
91	Hal	1	1	5
93	Cyclo	1	5	0
97	Hal	2	4	2
98	Hal	4	3	0
99	Hal	3	2	0
100	Hal	4	3	2
122	Hal	2	0	5
127	Other	1	4	0
135	Cyclo	1	4	0
156	Cyclo	1	5	0
185	Hal	1	4	0
205	N-B	1	3	3
222	Ether	2	4	0
223	Other	0	4	1
234	N-B	0	4	0
255	Hal	2	0	4
328	Cyclo	3	0	1
338	N-B	1	5	0
345	Hal	NOT SCORED BY PANEL ----------		**
352	Cyclo	0	4	0
363	Cyclo	1	4	0

*May score 5.
**Patient's chart submitted late.

*Prepared by William Dozier, Sacramento, California.

TABLE 19.--ETIOLOGY OF INTERMEDIATE HEPATIC NECROSIS ASSESSED BY PATHOLOGY PANEL

Case	Anesthetic practice	Number of pathologists scoring*		
		Consistent with drug-induced hepatic injury	Consistent with effects of shock, anoxemia, or sepsis	Consistent with effects of viral hepatitis
27	[illegible]	0	3	0
34	[illegible]	2	2	0
73	Hal	0	3	0
86	Hal	2	3	3
87	Hal	1	3	3
89	M-B	1	2	1
92	Cyclo	1	4	0
102	Other	1	5	0
111	Hal	2	1	4
112	Cyclo	1	4	0
118		2	4	2
119	Hal	1	3	0
130	Ether	0	4	0
134	Cyclo	1	4	0
188	Hal	0	5	0
190	Other	0	3	0
196	Hal	1	5	0
200	[illegible]	1	3	0
206	Hal	1	3	0
207	Hal	0	5	0
220	Cyclo	0	1	2
224	Cyclo	0	3	1
248	Cyclo	0	4	0
249	Hal	1	5	0
268	Cyclo	0	3	1
269	Hal	0	1	3
271	M-B	1	2	0
304	Hal	1	5	0
308	Cyclo	0	3	3
330	M-B	2	2	1
344	Cyclo	1	5	0
346	Ether	3	5	0
348	Cyclo	0	4	0
365	M-B	CHART NOT AVAILABLE		
366	Cyclo	0	5	0

*Any score 5.

Thirty-five abstracts of intermediate hepatic necrosis were available for review (Table 19). Twenty-seven cases were considered to be consistent with shock, anoxemia, or sepsis. One case (346) was also considered to be consistent with drug-induced hepatic injury. Five cases (86, 87, 111, 269, and 308) were consistent with the effects of viral hepatitis. Of these five, three (86, 87, and 308) also appeared in the shock category.

Clinical Review

The chart abstracts* of cases of hepatic necrosis were reviewed by an ad hoc group composed of one member of each of four medical disciplines.** Their purpose was to judge whether the degree and pattern of hepatic injury could be explained by a primary or contributory cause in the clinical history, necropsy summary, or both. Three members of the committee independently surveyed 193 abstracts (four missing) of massive and intermediate necrosis, and one member separately reviewed the 80 massive hepatic necrosis abstracts. Thus, all four members of the ad hoc committee reviewed 80 of the 82 cases of massive hepatic necrosis, and three members reviewed the abstracts of 113 cases of intermediate necrosis.***

In most of the cases there appeared to be adequate clinical explanation for the massive hepatic necroses observed at necropsy: shock, especially with prolonged use of vasopressors; overwhelming infection; severe and prolonged congestive heart failure; and pre-existing hepatic disease. In several cases, however, no adequate explanation was evident. Of the 80 massive hepatic necrosis cases, seven were considered unexplained by one member of the group (two involved halothane, four cyclopropane, and one Other); eight additional cases were considered unexplained by two members of the group (four involved halothane, one nitrous oxide-barbiturate, two cyclopropane, and one Other); and nine cases were considered to be unexplained by three or four members of the group (Table 20). Of those nine, seven patients had received halothane for the final operation, one cyclopropane, and one Other. Of the nine patients, five had undergone one or more previous operations within 6 weeks of the final procedure. Of those five, four had received halothane on at least two occasions and the fifth had received ethylene for the final operation and ether for a previous operation.

Of the 113 cases of intermediate hepatic necrosis reviewed by three members of the group, 10 cases were considered unexplained (Table 21) by two or three members of the group; seven of the 10 patients had received halothane. Four of the 10 had undergone one or more previous operations within 6 weeks of the final procedure, and two of those four had received halothane more than once.

Table 22 summarizes the 71 cases of death from massive hepatic necrosis that were considered by more than one member of the group to be explained by clinical circumstances. This group included a high proportion of complicated operative procedures, and one-third were known to have hepatic disease or gave a history of alcoholism before operation.

Table 23 summarizes the 103 cases of death with intermediate necrosis that were considered by more than one member of the group to be explained by clinical circumstances. This group also contained a high proportion of complicated operative procedures. History of hepatic disease or alcoholism was prominent. Thirty of the 103 patients had pre-existing hepatic disease and six had a history of alcoholism; 35 underwent thoracic or cardiac surgery.

HALOTHANE LESION

Because considerable data were available on the histologic features of the 82 cases of massive hepatic necrosis, attempts could be made to ascribe a specific lesion to halothane. One approach is discussed in Chapter III-2. This section discusses the use of discriminant analyses to identify

*Summaries of 80 cases of massive hepatic necrosis are appended to this chapter.

**J. P. Bunker, C. G. Child, C. Davidson, and E. Gall.

***No clinical histories for cases 647 and 817 (massive) or 365 and 811 (intermediate).

TABLE 20.--SUMMARY OF "UNEXPLAINED" CASES OF MASSIVE HEPATIC NECROSIS*

Case	Age, years	Sex	Anesthetic practice	Contributing factor	Operative procedure(s)	Total no. ops. within 6 wks	Day of postop. jaundice**	Day of death following operation**	Previous exposure to halothane
55	72	M	Other***		Cholecystectomy; control postop. hemorrhage	2	No jaundice	2-2	
64	70	F	Hal		Cholecystectomy and biopsy liver-normal	1	14	20	
91	66	F	Hal		Excision skin ca., popliteal area; debridement and graft	2	26-3	31-8	Yes - 1
97	67	M	Hal	Alcoholism	Closure perf. ulcer; subtotal gastrectomy	2	19-9	19-9	Yes - 1
98	16	F	Hal		Repair lacerated tendons of wrist	1	No jaundice	14	
99	21	M	Hal		Craniotomy with biopsy; ventriculojugular shunt	2	No jaundice	14-5	Yes - 1
122	58	F	Hal		Endoscopy; cholecystectomy and repair of hiatus hernia; debride, & pack. of wound; resuture wound dehiscence	4	30-24-5-1	34-28-9-5	Yes - 3
255	45	F	Hal		Laparotomy and biopsy	1	28	35	
352	75	M	Cyclo		Laparotomy and release of adhesions	1	1	1	

*Three or 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 without knowledge of anesthetic agents used, although four cases had been publicized in the literature.
**Time following each operation listed.
***Cholecystectomy, nitrous oxide and ether; control postoperative hemorrhage, ethylene.

TABLE 21.--SUMMARY OF "UNEXPLAINED" CASES OF INTERMEDIATE HEPATIC NECROSIS

Age, years	Sex	Anesthetic practice	Contributing factor	Operative procedure(s)	Total no. ops. within 6 weeks	Day of postop. jaundice	Day of death following operation	Previous exposure to halothane
71	F	Hal	Jaundice 1-1/2 yrs before surgery	Open red. femur	1	5	24	
33	M	Hal		Carotid arteriogram-brain biopsy; carotid arteriogram; ventriculogram pneumoence-phalogram-brain biopsy	3	11-2-1	19-10-7	Yes - 1
40	M	Hal		Excision of tumor-shoulder; re-exploration for hemostasis	2	7-3	10-6	Yes - 1
39	F	Ether	Recent transfusions	Radical hysterectomy	1	No jaundice	13	
63	F	Hal		D & C	1	3	29	
63	F	N-B	Jaundice	Cholecystectomy common duct	1	Preop.	7	
43	F	Hal		Sigmoid colostomy	1	6	9	Yes - 1
39	F	Ether	Transfusions 4 months before surgery	Biopsy of the pelvic mass; expl. lap., biopsy of peritoneal implant	2	No jaundice	13-12	
44	M	Hal		Right upper lobectomy; closure of dehiscence	2	No jaundice	32-22	
60	F	Hal	Recent cytoxan therapy	Open femur	1	No jaundice	29	

TABLE 22.--SUMMARY OF EXPLAINED CASES OF MASSIVE HEPATIC NECROSIS

Case	Anes. prac.	Last gen. anes. to death	Oper.	No. of ops. in last 4 yrs	Mos. to prev. surg.	Prev. hal.	History of alcohol	Preop. hepatic dis. and/or jaundice	Jaundice before death
1	Hal	3	20	2	1,1	1	Unknown	No	Yes
36	Hal	5	90	4	1,1,1,1	5	Unknown	No	Yes
44	Hal	3	27	2	1,1	1	Yes	No	Yes
100	Hal	10	44	1	1	1	Unknown	No	Yes
185	Hal	1	59	1	1	0	Unknown	Yes	Yes
345	Hal	7	12	1	1	0	Yes	No	Yes
609	Hal	2	33	0	0	0	No	No	No
636	Hal	3	34	1	1	1	Unknown	No	No
653	Hal	2	33	0	0	0	Unknown	No	No
657	Hal	1	33	0	0	0	No	No	No
658	Hal	3	33	0	0	0	Unknown	Yes	Yes
660	Hal	1	34	0	0	0	Unknown	No	No
666	Hal	4	33	2	2,2	0	Yes	Yes	Yes
667	Hal	3	44	1	6	0	Unknown	No	Yes
681	Hal	2	58	0	0	0	Unknown	No	No
691	Hal	11	71	1	1	1	Unknown	No	No
711	Hal	7	45	2	1,1	0	Unknown	No	No
716	Hal	2	59	0	0	0	Unknown	Yes	Yes
723	Hal	42	12	1	27	0	Unknown	Yes	Yes
205	N-B	8	42	0	0	0	Unknown	Yes	Yes
222	N-B	5	33	0	0	0	Unknown	No	Yes
234	N-B	11	57	0	0	0	Unknown	No	Yes
338	N-B	9	33	0	0	0	Unknown	No	No
619	N-B	1	33	0	0	0	No	No	No
664	N-B	1	33	0	0	0	Unknown	Yes	No
665	N-B	0	42	0	0	0	Unknown	Yes	No
687	N-B	4	44	1	1	0	Unknown	No	Yes
689	N-B	8	27	0	0	0	No	No	No
709	N-B	2	33	4	1,2	0	Unknown	Unknown	No
712	N-B	5	33	0	0	0	Unknown	No	Yes
713	N-B	2	33	0	0	0	No	No	No
724	N-B	4	33	1	22	0	Unknown	Unkown	No
807	N-B	15	27	0	0	0	Yes	No	No
824	N-B	3	33	0	0	0	No	No	No
72	Cyclo	2	44	0	0	0	Unknown	No	No
74	Cyclo	9	45	0	0	0	Unknown	Yes	Yes
81	Cyclo	8	40	0	0	0	No	Yes	Yes
93	Cyclo	3	44	2	1,1	0	Unknown	No	No
135	Cyclo	2	57	0	0	0	Unknown	No	No
156	Cyclo	2	44	1	1	0	Unknown	Unknown	Unknown
328	Cyclo	40	62	0	0	0	Unknown	No	Yes
363	Cyclo	4	47	0	0	0	Yes	Yes	Yes
605	Cyclo	9	41	0	0	0	Unknown	Yes	Yes
620	Cyclo	3	33	0	0	0	No	No	No
645	Cyclo	8	57	0	0	0	No	No	No
650	Cyclo	19	27	1	20	0	Unknown	No	Yes
651	Cyclo	2	44	1	13	0	No	Yes	Yes
669	Cyclo	0	45	0	0	0	Unknown	Yes	No
670	Cyclo	0	57	1	26+	0	Unknown	Yes	No
673	Cyclo	14	48	1	3	0	Unknown	Yes	No
675	Cyclo	27	80	2,	1,2	0	Unknown	No	No
680	Cyclo	17	01	0	0	0	Unknown	No	No
686	Cyclo	0	36	0	0	0	Unknown	No	No
688	Cyclo	2	47	1	47	0	Unknown	No	No
692	Cyclo	0	57	0	0	0	Unknown	No	No
719	Cyclo	8	44	1	1	0	Unknown	No	No
802	Cyclo	2	59	0	0	0	Yes	No	Yes
812	Cyclo	6	45	0	0	0	Yes	Yes	No
618	Ether	2	44	0	0	0	No	No	No
685	Ether	7	47	0	0	0	Unknown	No	No
718	Ether	10	45	0	0	0	Unknown	No	No
51	Other	11	45	1	2	1	Yes	No	Yes
68	Other	1	44	2	1,1	0	Unknown	No	No
127	Other	8	47	0	0	0	Unknown	No	No
223	Other	3	57	0	0	0	Unknown	No	No
616	Other	3	45	1	1	0	Unknown	Yes	No
628	Other	1	33	0	0	0	No	No	No
632	Other	2	33	1	13	1	No	No	No
649	Other	3	57	1	1	0	Yes	No	No
707	Other	3	36	2	1,7	0	Unknown	No	No
717	Other	25	57	2	1,1	0	Unknown	No	No

TABLE 23.--SUMMARY OF EXPLAINED CASES OF INTERMEDIATE HEPATIC NECROSIS

Case	Anes. prac.	Last gen. anes. to death	Oper.	No. of ops. in last 4 yrs	Mos. to prev. surg.	Prev. hal.	History of alcohol	Preop. hepatic dis. and/or jaundice	Jaundice before death
73	Hal	1	76	2	1,1	0	No	No	Yes
87	Hal	7	41	3	10,11,26	1	No	Yes	Yes
119	Hal	17	16	1	1	1	No	No	Yes
188	Hal	5	34	1	1	0	Yes	No	No
196	Hal	2	34	1	1	1	No	No	No
206	Hal	8	48	1	13	0	No	Yes	No
207	Hal	2	45	0	0	0	No	No	No
249	Hal	5	42	0	0	0	No	No	Yes
601	Hal	10	65	0	0	0	No	No	No
607	Hal	6	33	0	0	0	No	No	No
611	Hal	28	34	0	0	0	No	Yes	Yes
612	Hal	5	45	1	18	0	No	No	No
617	Hal	6	66	3	5,7,16	1	No	No	No
622	Hal	15	12	2	1,17	1	No	No	Yes
626	Hal	0	33	0	0	0	No	No	No
629	Hal	5	33	0	0	0	No	No	No
630	Hal	1	33	0	0	0	No	No	No
631	Hal	0	33	0	0	0	No	No	No
633	Hal	1	33	1	1	1	No	Yes	No
634	Hal	3	12	0	0	0	No	No	No
635	Hal	3	33	0	0	0	No	No	No
637	Hal	3	33	0	0	0	No	No	No
648	Hal	6	36	1	1	1	No	No	No
652	Hal	15	99	0	0	0	No	No	No
654	Hal	3	33	1	2	1	No	No	No
661	Hal	2	27	4	1,1,5,8	0	No	No	Yes
668	Hal	1	57	0	0	0	No	No	No
676	Hal	9	27	0	0	0	No	No	No
678	Hal	28	27	0	0	0	No	No	No
684	Hal	7	02	1	42	0	No	No	No
690	Hal	4	88	1	1	1	No	No	No
695	Hal	11	75	2	1,3	2	No	No	No
696	Hal	1	33	2	6,23	0	No	Yes	No
697	Hal	8	33	0	0	0	No	No	No
703	Hal	0	34	0	0	0	No	Yes	No
721	Hal	4	27	0	0	0	No	No	No
801	Hal	11	80	1	53	0	No	No	No
803	Hal	2	33	0	0	0	No	No	No
805	Hal	13	41	0	0	0	No	Yes	Yes
821	Hal	9	34	0	0	0	No	Yes	Yes
823	Hal	13	05	1	1	0	No	No	No
89	N-B	24	41	0	0	0	No	Yes	Yes
330	N-B	1	45	0	0	0	No	Yes	Yes
621	N-B	14	52	1	1	0	No	No	No
624	N-B	2	12	0	0	0	No	No	No
625	N-B	1	47	3	1,1,1	0	No	No	Yes
640	N-B	25	70	1	3	0	No	No	No
644	N-B	2	16	0	0	0	No	No	No
655	N-B	1	25	0	0	0	No	Yes	No
706	N-B	2	33	1	1	1	No	No	No
710	N-B	9	73	1	10	0	No	No	No
725	N-B	4	33	0	0	0	No	No	No
804	N-B	7	48	0	0	0	No	No	Yes
806	N-B	4	48	1	1	0	Yes	No	No
814	N-B	3	47	0	0	0	No	No	No
815	N-B	2	33	0	0	0	No	Yes	No
816	N-B	1	33	2	7,27	0	No	Yes	No
7	Cyclo	12	50	0	0	0	No	No	No
34	Cyclo	19	59	0	0	0	No	Yes	Yes
92	Cyclo	5	33	2	17,17	0	No	Yes	Yes
112	Cyclo	5	44	1	1	1	No	No	Yes
134	Cyclo	13	33	0	0	0	No	Yes	Yes
200	Cyclo	5	60	0	0	0	No	Yes	No

Table 23 (Cont'd)

Case	Anes. prac.	Last gen. anes. to death	Oper.	No. of ops. in last 4 yrs.	Mos. to prev. surg.	Prev. hal.	History of alcohol	Preop. hepatic dis. and/or jaundice	Jaundice before death
220	Cyclo	6	45	1	24	0	No	Yes	Yes
224	Cyclo	8	20	0	0	0	Yes	Yes	Yes
248	Cyclo	2	44	0	0	0	Yes	Yes	Yes
268	Cyclo	2	44	0	0	0	No	Yes	Yes
308	Cyclo	3	44	0	0	0	No	No	Yes
344	Cyclo	2	47	0	0	0	No	No	No
348	Cyclo	2	44	0	0	0	No	Yes	Yes
366	Cyclo	2	45	0	0	0	No	No	No
608	Cyclo	23	52	3	2,7,9	0	Yes	No	No
615	Cyclo	10	88	1	14	0	No	No	No
671	Cyclo	4	57	0	0	0	No	No	No
672	Cyclo	5	33	1	22	0	No	No	No
693	Cyclo	7	36	0	0	0	No	No	No
694	Cyclo	1	33	1	29	0	No	No	No
702	Cyclo	4	65	0	0	0	No	Yes	Yes
704	Cyclo	2	34	2	1,1	0	No	No	No
715	Cyclo	41	50	2	10,19	0	No	Yes	No
822	Cyclo	7	95	3	1,1,3	2	No	Yes	No
639	Ether	7	57	0	0	0	No	No	No
642	Ether	18	75	0	0	0	No	No	No
679	Ether	0	33	0	0	0	Yes	Yes	Yes
698	Ether	3	44	0	0	0	No	Yes	Yes
808	Ether	4	47	0	0	0	No	No	No
820	Ether	38	58	0	0	0	No	No	No
102	Other	1	44	0	0	0	No	No	No
190	Other	7	33	1	1	1	No	No	No
600	Other	2	42	1	9	1	No	Yes	Yes
604	Other	2	92	2	1,36	1	No	No	No
613	Other	2	57	1	1	0	No	No	No
614	Other	2	33	0	0	0	No	Yes	No
623	Other	2	33	0	0	0	No	Yes	No
627	Other	9	70	0	0	0	No	No	No
638	Other	1	44	0	0	0	No	No	No
659	Other	4	36	1	1	1	No	No	No
663	Other	1	22	2	1,1	0	No	No	No
674	Other	12	88	1	2	0	No	No	No
683	Other	33	27	0	0	0	No	No	No
699	Other	4	44	0	0	0	No	No	No
722	Other	32	12	0	0	0	No	No	No
818	Other	5	40	0	0	0	No	No	No

the histologic variables that are the best index of discrimination between two groups. For this analysis, the 82 cases of massive hepatic necrosis were divided into a halothane group* and a "no halothane" group. Within these groups, the scores of the Pathology Panel were pooled for each histologic variable (Form IV).

The initial scoring by the Pathology Panel was done without specific instruction on protocol; therefore, there were blanks on the forms for many of the variables. It is difficult to tell whether the blanks represent zero scores or missing information. Consensus scores for each variable (five pathologists scoring) were calculated. Most of the variables on Form VI were scored on the basis of presence or absence, but some** were scored on the basis of degree (0 to 4+).

*Exposure to halothane any time within 6 weeks before death.

**Autolysis, necrosis, lobular inflammation, lobular bile stasis, portal inflammation, and portal bile stasis.

Six of the 53 histologic variables tested seemed to help discriminate between the two groups. They were, in order of significance:

(1) lipofuscin pigmentation in Kupffer's cells,
(2) lobular polymorphonuclear cytosis,
(3) acidophilic bodies in necrotic areas,
(4) degree of inflammation in portal triads,
(5) lobular lymphocytosis, and
(6) portal triad lymphocytosis.

Lobular polymorphonuclear cytosis was the only significant variable oriented with "no halothane."

Many of the cases selected preferentially by this analysis did, in fact, involve halothane, and most of these are the unexplained cases of massive hepatic necrosis. The inherent weakness of this analysis is that, when the number of factors (53) approaches the number of individuals studied, random variations may easily be mistaken for real differences, and there is no statistical or practical way of resolving this problem without accumulating more cases.

APPENDIX TO CHAPTER III-1
SUMMARIES OF 80 CASES OF MASSIVE HEPATIC NECROSIS*

SUMMARY OF CASE 1

History: This 67-year-old man entered the hospital with a 6-week history of dysphagia, 20-lb weight loss, and hoarseness.

X-rays taken before he came to the hospital showed ulcerating lesion in the lower third of the esophagus. Before he entered the hospital, procedure 1, consisting of esophagoscopy and biopsy, which showed carcinoma, had been done on an outpatient basis. This procedure was done under general anesthesia with premedication of: atropine, 0.4 mg; Phenergan, 25 mg; and Demerol, 25 mg. The anesthesia lasted 10 min and was general. Blood pressure at this time was 160/80, and the procedure was well tolerated.

Physical Examination: He was thin, was not jaundiced, had unequal pupils, and had no abdominal mass or tenderness.

Clinical Course: Twelve days after procedure 1, he underwent procedure 2, consisting of insertion of a Celestin tube as a palliative measure into the esophagus via a laparotomy performed under general anesthesia. After this, he was confused and anorectic, ate poorly, coughed poorly, and cooperated poorly. He was given radiation therapy with cobalt in 14 treatments from the 9th to the 25th day after procedure 2.

On the 25th day after procedure 2, x-rays showed that the tube was out of place, lying above the lesion in the esophagus, and he underwent procedure 3, consisting of esophagoscopy under general anesthesia, only to remove the tube. Very shortly after, he developed a marked shivering and tachycardia, with a pulse rate as high as 140 and wide swings in his temperature from 99 to 103 down to 94 F. He developed abdominal rigidity, but no crepitus in the neck or definite evidence of perforation of the esophagus. He was treated with oral fluids, intravenous fluids, and tetracycline, and was first noted to be jaundiced on the day he died, i.e., the 3rd day after procedure 3, or 28 days after procedure 2.

Necropsy Findings:

1. Recent insertion of Celestin tube for carcinoma of the esophagus.
2. Carcinoma of the esophagus with no gross extension locally or lymph node involvement.
3. Subhepatic abscess in the region of the pylorus and involving the lesser peritoneal cavity.
4. Pulmonary edema.
5. Extensive central necrosis of liver.

SUMMARY OF CASE 36

History: This 25-year-old man was well until 4 hr before admission, when his shirt caught fire while he was pouring gasoline into the carburetor of an automobile.

Physical Examination: He was well nourished and had third-degree burns estimated at 55 to 60 percent of his body surface area, including face, chest, back, and arms. There was no jaundice. The abdomen was not examined because of the presence of burns. The blood pressure was never taken because of the presence of burns on the upper extremities.

Clinical Course: He was treated with fluids and electrolytes, blood, and several dressing changes. Sixteen days after admission to the hospital, he had autografting from both thighs to the right arm. Six days after this, he started to have hallucinations and at this time was first noted to be jaundiced. This was thought to be due either to septicemia or to a transfusion reaction. Seven days postoperatively, an x-ray showed free air under the diaphragm and he was thought to have perforation of a Curling's ulcer. He died shortly after this, 7 days after operation, 23 days after admission to the hospital.

Necropsy Findings:

1. Third-degree burns of 60 percent of body surface area.
2. Severe central necrosis of liver, toxic.
3. Multiple superficial mucosal erosions of the stomach and duodenum.
4. No perforation of the gastrointestinal tract or other explanation of the free air under the diaphragm seen by x-ray was found at necropsy.

SUMMARY OF CASE 44

History: This 64-year-old man had a history of alcoholism, a myocardial infarction 5 years previously, and angina pectoris since the myocardial infarction. He had been studied in another hospital 3 weeks before and been found to have a left upper lobe lesion in his chest. He was admitted for elective surgery.

Physical Examination: He was not jaundiced and there was no abdominal mass or tenderness. Blood pressure was 140/90.

Clinical Course: One day after admission to the hospital, he had bronchoscopy under local anesthesia, which showed an irregularity of the orifice of the left upper lobe; this area was biopsied and

*Anesthetic agent not included in these summaries to allow unbiased clinical and pathologic review. Anesthetic practices are listed in Tables 20 and 22 of Chapter III-1.

showed only chronic inflammation. Three days after admission to the hospital, he underwent procedure 1, consisting of left upper lobectomy for what proved to be a chronic granuloma. After this, he had confusion thought to be due to delirium tremens, chest pain, fever, continued drainage leaking and bubbling in his chest tube, and transient hypotension the 1st and 2nd days to a pressure of 70, for which a cause was never found. He also had transient atrial fibrillation. Eleven days after procedure 1, x-rays showed a left hydropneumothorax with a radiopaque foreign body remaining in the chest.

Twelve days after procedure 1, he underwent procedure 2, consisting of a removal of a surgical sponge. After procedure 2, he remained febrile, hypotensive, cyanotic, confused, incontinent, and unable to clear secretions effectively. On the 4th day, he vomited blood, complained of chest pain, and died 1.5 hr after the final complaint of chest pain, 3 days after procedure 2, 14 days after procedure 1, and 18 days after admission to the hospital. He was jaundiced only during the last day of life.

Necropsy Findings:

1. Left serosanguineous pleural effusion, 200 cc.
2. Bilateral pulmonary atelectasis.
3. Pulmonary edema.
4. Recent thromboemboli in branches of both lower lobe pulmonary arteries.
5. Aspiration of gastric contents.
6. Acute hepatitis with marked acute central hemorrhagic necrosis.
7. Healed myocardial infarction.

SUMMARY OF CASE 51

History: This 49-year-old man entered the hospital the second time for elective surgery for duodenal ulcer.

He had been in the same hospital 6 weeks previously for closure of a perforated ulcer. This first operation, procedure 1, was done under general anesthesia, lasting 1 hr and proceeding uneventfully. His postoperative course was uneventful and he was discharged in 10 days. A BSP test during that hospitalization showed 36 percent retention in 30 min. No other studies pertaining to liver function were done.

He also had a history of alcoholism in the past, but allegedly the alcoholic intake had been moderate recently.

He was re-admitted for elective, definitive surgery for his duodenal ulcer after being treated with Pro-banthine, Gelusil, and phenobarbital because of continuing abdominal distress. Physical examination was negative except for the presence of moderate follicular acne. Blood pressure was 110/80.

Clinical Course: He was studied and treated in the hospital for 4 days before surgery. He was treated with antibiotics (penicillin and tetracycline) because of the presence of acne.

On the 5th day, under anesthesia, he underwent a 4-hr operation, strengthening the closure of the duodenal stump and gastrojejunostomy. The operation entailed a 600-cc blood loss; no blood was given, but a transfusion of 500 cc of albumin. This operation also proceeded uneventfully.

On the 2nd postoperative day, he was found to be jaundiced. The jaundice deepened and he had chills and fever, and developed liver flap and coma, and finally upper gastrointestinal bleeding. He continued to have bile in his nasogastric return, as well as in his stool. His treatment included steroids, blood, gastric cooling, and fibrinogen, but he died 10 days after the second operation.

Necropsy Findings:

1. Acute atrophy of liver, etiology viral hepatitis.
2. Peritonitis, localized lesser peritoneal sac.
3. Incompetent duodenal stump, etiology surgical operation with perforation of duodenal stump and drainage of duodenal contents into lesser peritoneal sac.
4. Necrotizing bronchopneumonia with abscess formation left and right lungs.
5. Acute and chronic bronchitis.
6. Pulmonary emphysema.
7. Pleural effusion, bilateral.
8. Acute congestion of kidney, marked, bilateral.
9. Cholemic nephrosis.

SUMMARY OF CASE 55

History: This 72-year-old man entered the hospital for elective cholecystectomy.

Two months earlier, he had been in the hospital for resection of a carcinoma of the sigmoid colon; at that time he was found to have an acute cholecystitis for which a cholecystostomy had been done under an unknown type of anesthesia; no details about that hospitalization are available.

Postoperatively he did well, and the cholecystostomy tube had come out 2 weeks before the final admission. He had been on no medications and had not been jaundiced.

Physical Examination: He was well developed and well nourished and had no abdominal mass, tenderness, or jaundice. Blood pressure was 140/75.

Clinical Course: On the day after admission, a cholecystectomy and biopsy of a suspicious nodule in the liver were performed under general anesthesia, and proceeded uneventfully. Postoperatively, on the afternoon of surgery, he became hypotensive and showed abdominal distention, so

he was returned to surgery for a second operation that same night, also under general anesthesia. At this operation, he was found to be bleeding from multiple points throughout the abdomen. In spite of transfusion of a total of at least 14 units of blood, he showed bleeding from the rectum, the mouth, the wound, the nasogastric tube, and needle puncture sites; he died 36 hr after the second operation. He was hypotensive on vasopressors most of this time and was oliguric after the second operation. He never became jaundiced.

Necropsy Findings:

1. Hemoperitoneum, 3000 cc, associated with generalized bleeding tendency.
2. Acute massive necrosis of hepatic parenchyma.
3. Bilateral pleural effusions, total 3000 cc.
4. Bilateral pulmonary atelectasis, edema, congestion, and hemorrhage.
5. Generalized ecchymosis of peritoneum, liver, diaphragm, small and large intestine, omentum, and mesentery.
6. Hemorrhage into spleen.
7. Ecchymosis of skin at injection sites.

SUMMARY OF CASE 64

History: This 70-year-old woman entered the hospital for elective cholecystectomy with a history of several years of right upper quadrant distress and intolerance of fatty foods.

She had never been jaundiced, and was known to have arteriosclerotic heart disease, Meniere's syndrome, and seborrheic dermatitis of the scalp, for which she had been on unknown medications. She had been studied in an out-patient clinic, whose records are not available, and there had had x-rays and blood tests that were completed 4 weeks before her hospital admission.

Physical Examination: She was well nourished, was not jaundiced, and had no abdominal mass or tenderness. Blood pressure was 170/80.

Clinical Course: One day after admission to the hospital she underwent cholecystectomy and liver biopsy. The liver biopsy showed "minimal lipid infiltration." After surgery she did quite well, and was discharged on the 7th day.

Seventeen days after surgery she was readmitted with a history that 14 days postoperatively she had become jaundiced and after that had developed light stools, nausea, vomiting, and abdominal pain, and had vomited dark blood. She was admitted in coma, with no abdominal mass or tenderness, passing dark bloody material by rectum, with a stiff neck, and with paralysis of the right side of the face and left lower extremity. She was thought by a neurologic consultant to have intracranial hemorrhage; lumbar puncture showed 40-50 RBC per high-power field.

After her admission, 17 days following surgery, the stiff neck cleared, the paralysis extended to all four extremities, and she became hypotensive in spite of the transfusion of blood. She became more deeply jaundiced, gradually deteriorated, became oliguric, and died 21 days after her original admission to the hospital, 20 days after surgery, 3 days after her readmission to the hospital, and 6 days after the onset of jaundice.

Necropsy Findings:

1. Severe acute hepatitis with fatty infiltration of the liver.
2. Massive melena due to acute gastric ulcers (six) and petechiae.
3. Hemorrhagic ascites, 300 cc.
4. Acute erosive esophagitis.
5. Aspiration of gastric contents.
6. Right pleural effusion, 300 cc.
7. Examination of brain not permitted.

SUMMARY OF CASE 68

History: This 42-year-old man was transferred from another hospital 2 days after he had been injured in a crushing injury when an automobile fell off the jack while he was lying under it working.

In the original hospital he arrived in shock and was found to have a compound fracture of the left radius, separation of the pubic symphysis, separation of the right iliac joint, hemoperitoneum, and disruption of the small intestine with massive intraperitoneal and retroperitoneal hemorrhage. He was taken to surgery under general anesthesia, and underwent open reduction and internal fixation of the fracture of the radius, evacuation of massive hemoperitoneum, and small bowel resection. This operation lasted 4.5 hr and during this time he had no blood pressure for at least 1 hr. During this procedure, he received 15 units of blood.

Postoperatively, he was completely anuric, had considerable respiratory difficulty, and required four more units of blood. After 48 hr in the first hospital, he was transferred by air, with blood, oxygen, and Levophed running, to the second hospital.

Physical Examination: He was obese, was semicomatose, and had inadequate respirations. Blood pressure was 100/?. Pulse was 110. Abdomen was hidden by dressings.

Clinical Course: He immediately received respiratory assistance by means of endotracheal intubation and very shortly had tracheostomy performed under local anesthesia. Because of a rising potassium level, he had hemodialysis on an artificial kidney. After 1 day in the second hospital he developed cardiac arrest; he responded to cardiac massage, but immediately after this was found to have abdominal distention and hypotension thought to be due to progressive intra-abdominal bleeding.

Accordingly, he had his second operation, again under general anesthesia, with the evacuation of 1500 cc of intraperitoneal and retroperitoneal blood, but without transfusion. After this

operation, he remained hypotensive and again, because of a rising serum potassium level, a second hemodialysis was started 9 hr after the end of the second operation. He became hypotensive and suffered cardiac arrest during his second hemodialysis and died 11 hr after the end of the second operation. Jaundice was not reported in life but was noted at necropsy.

Necropsy Findings:

1. Acute massive necrosis of the liver.
2. Hemorrhagic necrosis of the gallbladder.
3. Multiple small infarcts, large and small intestine.
4. Acute tubular necrosis of the kidneys, bilateral.
5. Fracture of the pubic symphysis.
6. Fracture of the left radius.
7. Multiple intracerebral petechiae.
8. Cerebral edema.

SUMMARY OF CASE 72

History: This 43-year-old woman was admitted to the hospital with a history of an abdominal mass developing over a period of 9 months. There had been a 10-lb weight loss but no other symptoms.

Physical Examination: She was thin and not jaundiced. A large, rounded mass filled the entire abdomen. The liver, as such, was not palpable.

Clinical Course: She was studied and prepared in the hospital for 7 days, her preparation including transfusion of 1500 cc of blood. After a week in the hospital, she underwent exploratory laparotomy in which a tumor mass was found extending from the diaphragm to the pelvis. This was interpreted as being bilateral horseshoe kidneys with fusion in the midline. Nothing definitive was done and the abdomen was closed.

After the operation, the patient had practically no urine output and remained hypotensive and unresponsive in spite of intensive management for renal failure. She was not noted to be jaundiced in life. She died 48 hr after surgery, 8 days after admission to the hospital.

Necropsy Findings:

1. Retroperitoneal sarcoma, low-grade malignant schwannoma, 9270 g, unrelated to any intra-abdominal viscera. (The kidneys were normal.)
2. Massive necrosis of the liver (shock).
3. Hemoglobinuric nephrosis.
4. Moderate left hydronephrosis and hydroureter.
5. Focal adrenal cortical necrosis.
6. Pulmonary atelectasis, congestion, and edema.

SUMMARY OF CASE 74

History: This 36-year-old woman entered the hospital because of vomiting blood. For the preceding 6 months, she had been ill with fever, anemia, edema, joint pains, muscle tenderness, paresthesias, and muscle spasms. She had been admitted and studied extensively on the medical service 1 month before the final hospital admission. Laboratory tests at that time included: total protein, 4.4; albumin, 3.1; globulin, 1.3; BSP retention, 22 percent; alkaline phosphatase, 7.5; SGOT, 76; and SGPT, 42. She had bone marrow, skin, and muscle biopsies, but the only diagnosis reached was "collagen disease." She was discharged on prednisone, 60 mg/day, aspirin, and antacids. On this medicine, she developed hirsutism, increased appetite, obesity, and a buffalo hump. For 2 weeks before the final hospital admission, she had recurrent epigastric pain developing on an empty stomach, particularly in the middle of the night, and relieved by antacids. Two hours before the final admission, she abruptly vomited blood and began to pass blood by rectum. This was her first episode of gastrointestinal bleeding.

Physical Examination: She was pale but not jaundiced. Blood pressure was 110/60. Pulse was 170. She had a round face and increased body hair; the liver was palpable three fingerbreadths below the right costal margin.

Clinical Course: She was given 7500 cc of blood but the gastrointestinal bleeding continued. On the day of admission, she underwent her only operation, consisting of vagotomy, pyloroplasty, gastrostomy, suture ligature of a bleeding duodenal ulcer, and liver biopsy. The liver was said to be "enlarged and abnormal."

Immediately after the operation, she became jaundiced and continued to ooze from her incision. She continued febrile with temperature as high as 40 C and evidence of left lower lobe pneumonia. Jaundice deepened and on the 8th day she became hypotensive to 70/50 and developed leakage of dark brownish fluid around the gastrostomy. Her urine output was always good. She died 9 days after admission to the hospital, 9 days after surgery.

Necropsy Findings:

1. Centrilobular hemorrhagic necrosis of the liver, advanced with biostasis and regeneration of surviving liver plates.
2. Intrahepatic endophlebitis of hepatic veins with focal, partly organized mural and occlusive venous thrombi.
3. Acute intrahepatic pericholangitis, advanced.
4. Active duodenal peptic ulcer with bleeding.
5. Unhealed abdominal wound and wounds of pyloroplasty and gastrostomy (pyloroplasty separated at necropsy).
6. Generalized fibrinopurulent peritonitis.
7. Nonspecific focal myopathy, various muscles.

8. Focal nonspecific glomerulitis of kidneys.
9. Confluent hemorrhagic necrosis of the spleen.
10. Atelectasis of lungs, advanced.
11. Bilateral serosanguineous pleural effusion; right, 550 cc; left, 600 cc.
12. Chronic passive congestion of the liver and spleen.

SUMMARY OF CASE 81

History: This 59-year-old man was admitted with right upper quadrant distress.

Two months before the final admission, he had surgery in another hospital under an unknown type of anesthesia for bleeding duodenal ulcer. A subtotal gastrectomy was done. Ten units of blood were given. Further details concerning this hospitalization are not available.

One month before, he had a 5-day illness considered to be influenza, with chills and fever but no jaundice.

Physical Examination: He was well nourished, not jaundiced, and in moderate distress. Temperature was 99 F. Blood pressure was 120/80. There was moderate right upper quadrant tenderness, but no definite mass. During his first 3 days in the hospital, he had chills and fever as high as 104 F, as well as hiccups, nausea, and vomiting. He was described as critically ill, and was treated with nasogastric tube and antibiotics.

Clinical Course: On the 3rd day, a cholecystostomy was performed under anesthesia in a procedure lasting 0.5 hr. The gross appearance of the liver was not stated. He tolerated the procedure well, but in the recovery room it was thought, in retrospect, that he had been severely depressed by the procedure, in that it took him about 13 hr to recover from the anesthetic. On the 1st postoperative day, he was noted to be jaundiced, although the serum bilirubin level had been rising up to the time of surgery. He was treated with antibiotics and was able to eat, but developed progressive jaundice with dark urine and ecchymosis. On the 7th day, he was confused, and on the 8th day he abruptly became hypotensive with marked hyperventilation and acidosis. He was treated with vasopressors, steroids, and antibiotics, but died 8 days after the second operation and 11 days after the final hospital admission.

Necropsy Findings (provisional necropsy diagnosis based only on gross exam):

1. Acute hepatic necrosis, probable homologous serum hepatitis.
2. Acute cholecystitis with necrosis and gangrene of the gallbladder.

SUMMARY OF CASE 91

History: This 66-year-old woman entered the hospital for elective surgery for carcinoma of the right leg.

Forty-four years before, at the age of 21, she had sustained a burn in the right popliteal fossa that had never healed completely. There remained a small ulcerated area that had been enlarging for 4 months before the final admission to the hospital. She had been known to have diabetes mellitus for 16 months before the final admission and had been taking Orinase. It is not known whether she had it at the final hospital admission.

Physical Examination: She was obese but not jaundiced. Blood pressure was 130/70. There was no abdominal mass or tenderness. There was a 12 x 12-cm ulcerated fungating lesion in the right popliteal fossa.

Clinical Course: The first biopsy done under local anesthesia was not positive, but suggested early squamous cell carcinoma. A second biopsy done under local anesthesia was positive for squamous cell carcinoma.

Twenty-three days after admission to the hospital she had operation 1, consisting of excision of the lesion in the right popliteal region, including partial resection of the gastrocnemius muscle and application of split-thickness skin grafts. After this, she had a low-grade fever and was seen to have 75-80 percent take of the skin graft with some infection, which cleared with conservative treatment.

Twenty-three days after operation 1, she had operation 2. Both operations were under general anesthesia. Operation 2 consisted of debridement of the right popliteal region and split-thickness skin graft with pinch grafts. Three days after this, she became confused and then comatose. She developed jaundice with dark urine and a temperature of 103 F. The jaundice became deeper and in the last 3 days of life she was oliguric and the last day hypotensive. She died 54 days after admission to the hospital, 31 days after operation 1, and 8 days after operation 2.

Necropsy Findings:

1. Acute diffuse hepatic necrosis, etiology undetermined.
2. Diabetes.
3. Bilateral atelectasis, partial.
4. Mild pulmonary congestion.
5. Interstitial pancreatitis.

SUMMARY OF CASE 93

History: This 63-year-old man entered the hospital for elective repair of an abdominal aortic aneurysm that had been known to be present for 4 years.

He had a history of cardiac disease with angina and was taking digitalis and nitroglycerin.

Physical Examination: Blood pressure was not stated. There was no mass or tenderness in the right upper quadrant. A 14 x 17-cm aortic aneurysm was palpable in the abdomen.

Clinical Course: He was found to have a mild urinary tract infection and was treated with Gantrisin and Chloromycetin and maintained on digitalis. After 2 weeks in the hospital, he underwent operation 1 under spinal plus "general" anesthesia, consisting of resection of the abdominal aortic aneurysm and replacement with Teflon graft. During this procedure, he was given 10 million units of penicillin intravenously, and after this became abruptly hypotensive for a period of at least 45 min and was thought to have had a penicillin reaction. Postoperatively, he was hypotensive and passed several bloody stools.

One day later he was returned to surgery for operation 2, again under general anesthesia, and had evacuation of retroperitoneal hematoma and repair of an aortic suture line. Several dusky areas in the small intestine appeared to improve after procaine was infiltrated about the celiac plexus. After this operation he became hypotensive again with evidence of bleeding in the flank.

One day after the second operation he was returned to surgery for operation 3, under "general" anesthesia, and had laparotomy, evacuation of retroperitoneal hematoma, and tracheostomy. He was thought to have a coagulation defect and was given 2500 cc of bank blood and 1000 cc of fresh red blood.

After operation 3, he did well for 2 days, but he died suddenly 3 days after the last operation and 5 days after the first operation, with a cardiac arrhythmia. He was not noticed to be jaundiced.

Necropsy Findings:

1. Intraperitoneal hemorrhage, 1100 cc.
2. Retroperitoneal hemorrhage, 700 cc.
3. Pseudomembranous enterocolitis involving the entire small intestine, cecum, and rectum, probably on an ischemic basis.
4. Central lobular necrosis of the liver.
5. Acute tubular necrosis of the kidney.

SUMMARY OF CASE 97

History: This 67-year-old man entered the hospital with acute severe abdominal pain that began 8 hr before admission.

He had a long history of heavy alcohol intake, although allegedly this had been reduced recently. He had been having abdominal pain for 2 weeks and had been receiving Sparine, antacids, and laxatives in unknown amounts.

Physical Examination: He appeared acutely ill and was cyanotic. Temperature was 97 F, pulse was 60, and blood pressure was 110/70. He was not jaundiced. There was marked epigastric and right lower quadrant tenderness.

Clinical Course: He was taken to surgery on the day of admission and a perforated duodenal ulcer was closed under anesthesia. Aside from some respiratory problems, he did well for 10 days. Then, on the 10th day, he developed acute massive upper and lower gastrointestinal bleeding and was taken to surgery for a second operation, under anesthesia, in which a bleeding posterior duodenal ulcer was suture-ligated and a gastrectomy was performed. The procedure lasted 4.5 hr and he received 2000 cc of blood during surgery.

After this operation, he did well for about 4 days and then developed fever, then cyanosis, then oliguria. On the 9th postoperative day he was noted to be jaundiced. The fever, oliguria, and jaundice persisted in spite of antibiotics, fluid and electrolyte management, steroids, and blood, and he died 9 days after the second operation and 19 days after the first operation.

Necropsy Findings:

1. Acute submassive necrosis of the liver.
2. Nephrosis, marked.
3. Paraduodenal abscess, in continuity with a blown-out duodenal stump.
4. Recent coronary thrombosis with healing myocardial infarction.
5. Bilateral bronchopneumonia with pulmonary edema, congestion, and atelectasis.

SUMMARY OF CASE 98

History: This 16-year-old girl entered the hospital shortly after she fell through a glass door, sustaining a deep laceration of the right wrist.

Physical Examination: There was a deep laceration of the right wrist with evidence of laceration of several tendons. Blood pressure was 110/80. There was no jaundice or abdominal mass or tenderness.

Clinical Course: There was surgery shortly after admission and she had a 4-hr operation under general anesthesia, involving repair of eight lacerated tendons and a partial laceration of the median nerve. After this, she did well until the 9th postoperative day, when she developed a fever as high as 105 F. She continued with high fever, became more lethargic, and developed nausea, vomiting, and confusion. She never developed jaundice or abdominal mass or tenderness. She died 14 days after admission to the hospital.

Necropsy Findings:

1. Acute massive necrosis of the liver.
2. Nephrosis, severe.

SUMMARY OF CASE 99

History: This 21-year-old man entered the hospital with a 6-year history of headaches, which had become more severe in the preceding year. He also had recent onset of blurred vision, complete loss of vision, and transient staggering gait.

Physical Examination: He was moderately nourished and had no jaundice. Blood pressure was 120/80. He was mentally slow, and showed papilledema and bilateral visual field defects.

Clinical Course: In his first 2 weeks in the hospital, he underwent lumbar punctures and carotid arteriograms, then ventriculograms, then contrast ventriculograms, then bilateral ventriculostomy with subgaleal shunts, all performed under local anesthesia. His studies showed increased cerebral spinal fluid pressure and x-ray evidence of a tumor in the region of the third ventricle. He was started preoperatively on radiation therapy, about 300 r/day, along with INH, 100 mg three times a day, as an adjunct to radiation therapy. He became agitated and confused.

On the 13th day under anesthesia, he had right frontal craniotomy and was found to have an inoperable brain tumor. After this, he had fever, continuing evidence of increased spinal fluid pressure, and more confusion, incontinence, and poor nutrition. He was treated with steroids.

Nine days after the first operation, he had a second operation, again under anesthesia, consisting of a ventriculocaval shunt, shunting spinal fluid from ventricles through the jugular vein to the vena cava. After this, he remained confused, incontinent, difficult to manage, and hypotensive, with continuing evidence of spinal fluid pressure. On the last day of life, he bled from the nose and showed retinal hemorrhages, hemiplegia, bilateral fixed pupils, and moderate hypotension in spite of steroids. He died 5 days after the second operation, and 14 days after the first operation. He was never noticed to be jaundiced in life.

Necropsy Findings:

1. Astrocytoma, grade II midline and third ventricle, persistent, replacing and obstructing the third ventricle.
2. Intraventricular hemorrhage, right cerebral hemisphere.
3. Massive liver necrosis (infectious hepatitis).
4. Cerebral edema.
5. Pulmonary edema and congestion.

SUMMARY OF CASE 100

History: This 39-year-old Japanese man, who had been born in the United States but had lived in Japan for the last 15 years, had a 5-month history of indigestion and pain on an empty stomach with a 15-lb weight loss. One month before the final hospitalization, a laparotomy was performed in a hospital in Japan, where it was found that he had carcinoma of the stomach extending to the transverse colon, transverse mesocolon, and greater omentum. Nothing other than biopsy was done. No blood was given. One month after the laparotomy in Japan, he was admitted finally to a hospital in the United States for definitive surgery.

Physical Examination: He was well nourished and not jaundiced. There was a healing upper abdominal incision. No abdominal mass or tenderness was noted. Blood pressure was 140/80.

Clinical Course: Preoperatively, he was treated with blood and antibiotics. Three days after admission to the hospital, or 1 month after operation 1, he underwent operation 2, consisting of a total gastrectomy, splenectomy, and resection of the transverse colon, tail of the pancreas, and greater omentum for carcinoma of the stomach. It was later found that carcinoma extended to the proximal surgical margin.

Postoperatively he did well for the first 10 days, and then abruptly developed chills, fever to 40 C, and evidence of paralytic ileus or small bowel obstruction. He was treated with antibiotics and various small intestinal tubes. X-rays showed subphrenic abscess with associated small bowel obstruction.

Twenty-three days after operation 2, or about 2 months after operation 1, he had operation 3, consisting of incision and drainage of the left subphrenic abscess. Later, he deteriorated and became febrile. From the 3rd postoperative day onward, he was jaundiced, with confusion, depression, flapping, tremor, and finally convulsions and other neurologic symptoms. He died 10 days after after operation 3, 33 days after operation 2, 36 days after final admission to the hospital, and 2 months after operation 1.

Necropsy Findings:

1. Acute hepatitis.
2. Pulmonary edema, diffuse, marked.
3. Diffuse bronchopneumonia.
4. Gastrointestinal hemorrhage, marked, terminal.
5. Left subdiaphragmatic abscess with drain in place.

SUMMARY OF CASE 122

History: This 58-year-old woman entered the hospital for evaluation of multiple problems, including known cholelithiasis, a tumor of the left breast known for 20 years, and cardiac enlargement. She had no history of jaundice, cardiac symptoms, or cardiac failure.

Physical Examination: She was obese, had a palpable tumor in the left breast, had an umbilical hernia, was not jaundiced, had no abdominal mass or tenderness, and had a blood pressure of 160/90.

Clinical Course: X-rays confirmed the presence of gallstones and a hiatus hernia. The chest film showed cardiac enlargement, suggestive of pericardial effusion. She had four operations under general anesthesia. The first was esophagoscopy, a brief, uneventful procedure. The second, 6 days after the first, was the largest

operation, including excision biopsy of multiple fibroadenomata of the left breast, cholecystectomy with operative cholangiograms, which were normal, pericardial aspiration and pericardial biopsy performed through the diaphragm, hiatus hernia repair, and umbilical hernia repair. At this operation it was seen that the liver was normal.

After the second operation, she did well until the 12th day, when it was noted that there was separation of the midline abdominal wound down to the fascia. The wound was irrigated with hydrogen peroxide. Then 19 days after operation 2, she had operation 3, a brief procedure in which the abdominal incision was debrided and packed with iodoform gauze.

Operation 4 was 4 days after operation 3, and in this the packing was removed and the previously placed retention sutures were tied. Shortly after this, she became febrile to 103 F, with confusion progressing to coma and jaundice, which became deeper and was accompanied by liver flap. She became hypotensive the last 2 days of life, her urine output ceased, she had a tracheostomy under local anesthesia, and she remained deeply jaundiced. She died 5 days after operation 4, 9 days after operation 3, 28 days after operation 2, 34 days after operation 1, and 43 days after admission to the hospital.

Necropsy Findings:

1. Acute infectious hepatitis, with hepatic insufficiency and jaundice.
2. Pulmonary edema.
3. Diffuse fibrous pericarditis.
4. Edema of the kidneys.

SUMMARY OF CASE 127

History: This 44-year-old white man had been in the hospital 1 month before, at which time he had a 4-month history of anorexia, weakness, weight loss, abdominal cramps, and constipation, and a 2-month history of dyspnea on exertion and left chest pain. Before admission to the hospital, he had been treated with hexylresorcinol, for an unknown period in unknown dosages, for intestinal parasites. He was emaciated and had two firm masses in the right side of the neck, the biopsy of which showed metastatic undifferentiated carcinoma. X-rays showed a left upper lobe infiltrate and a 3 x 4-cm mass in the left hilum. The small bowel series was interpreted as showing narrowing and ulceration of the terminal jejunum, most likely malignant tumor. Laboratory tests included: PCV, 28; hemoglobin, 9.3; sedimentation rate, 60; WBC, 8600; alkaline phosphatase, 2.1; acid phosphatase, 0.441; SGOT, 8; SGPT, 6; BUN, 10; and uric acid, 3.1. Stool showed occult blood. Prothrombin time was 65 percent and rose to 100 percent with vitamin K. He was thought to have carcinoma, metastatic from the small intestine to the chest and cervical lymph nodes, and was treated with fluorouracil and then transferred to another hospital and finally to his home.

One month later, because of continued weakness and weight loss, progressive dyspnea and chest pain, and particularly regurgitation of food or vomiting, he was admitted finally.

Physical Examination: He was pale and cadaverous, weak, hoarse, and confused. Blood pressure was 98/60. He was not jaundiced. There was no abdominal mass or tenderness. There was dullness over the left half of the chest.

Clinical Course: On the 2nd hospital day, thoracentesis of 2300 cc was performed, with little improvement in his dyspnea. He continued to vomit and was thought to have small bowel obstruction. On the 4th hospital day he underwent exploratory laparotomy under general anesthesia and was found to have two obstructing lesions in the proximal ileum; these were bypassed with two side-to-side enteroenterostomies. He did well until the 6th postoperative day, when he developed evidence of pericardial effusion with cardiac tamponade. Pericardiocentesis was performed twice and nitrogen mustard was instilled into the pericardium. He did poorly after this, and died 1 day after the pericardiocentesis, or 8 days after the operation.

Necropsy Findings:

1. Adenocarcinoma, bronchogenic, left upper lobe bronchus, with metastases to hilar lymph nodes, pericardium, epicardium, adventitia of descending aorta, jejunum, mesenteric lymph nodes, periaortic lymph nodes, and right adrenal gland.
2. Pericardial effusion, 1100 cc; right pleural effusion, 600 cc; left pleural effusion, 900 cc; ascites, 400 cc.
3. Bronchopneumonia, left lung.
4. Congestion and edema, right lung.
5. Congestion, central, with necrosis, moderately severe, liver.

SUMMARY OF CASE 135

History: This 56-year-old white woman entered the hospital as an emergency because of acute pain in the right lower extremity. She had been well until 24 hr before the final admission, when she developed severe pain in the right shoulder and chest. This pain gradually decreased, but 12 hr before the final admission, she developed increasing pain in the right chest, the left side of the abdomen, and the right lower extremity.

Physical Examination: She was well nourished and in considerable distress. She was not jaundiced. Blood pressure was 140/80. There was no abdominal mass or tenderness. The right femoral pulse was absent. The right lower extremity was colder than the left.

Clinical Course: She was thought to have had an embolism to the right femoral artery and was taken directly to surgery. She had an embolectomy of the right common iliac artery and an appendectomy.

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Following surgery, the pulse, color, and temperature of the right lower extremity remained good, but she was found to have different blood pressures in the two arms (95/60 on the right and 75/50 on the left), and systolic murmur beneath the left clavicle. On the 2nd day, the left radial and the right dorsal pedal pulses became weaker, the murmur became louder, and finally she was found to have no blood pressure in the right arm. She died 2 days after surgery and admission to the hospital. She was never jaundiced.

Necropsy Findings:

1. Generalized arteriosclerosis.
2. Dissecting aneurysm of the ascending aorta with rupture and cardiac tamponade, 120 cc.
3. Focal atelectasis.
4. Central necrosis of the liver.
5. Infarction of the kidney, recent, right.

SUMMARY OF CASE 156

History: This 41-year-old man was readmitted to the hospital because of anemia and weakness.

He had been known to have myelogenous leukemia for 4 years. He had previously received radiation therapy to the spleen, radioactive phosphorus, Myleran, and numerous blood transfusions, although details of this treatment are not available.

He had been admitted to the hospital 7 months before the final admission because of weakness and dyspnea on exertion. At that time, the WBC was 3900; RBC, 3.29 million; hemoglobin, 9.2; and platelets, 394,000. He was treated with blood and radiation.

He had been admitted 4 months before the final admission. At that time, the WBC was 46,000; platelets, 700,000; and hemoglobin, 10.8. He was again treated with radiation to the spleen.

Physical Examination: He was well nourished but appeared to be chronically ill. He was pale but not jaundiced. The spleen was greatly enlarged, filling most of the abdomen.

Clinical Course: The patient had two operations, the first being an elective splenectomy and gastrostomy. The details of the preparation of this operation, the course of the operation, and the postoperative course are not available, but it is known that the patient developed intraperitoneal bleeding and had a second operation in which, apparently, it was impossible to control the bleeding, so that numerous packs and drains were left in. Details of blood pressure, urine volume, and the presence or absence of jaundice are not available. The chronologic relationships of surgery to death are not known, except for the fact that he died 3 days after the first operation. Slight jaundice was present at necropsy.

Necropsy Findings:

1. Hepatic necrosis, diffuse, moderately severe.
2. Chronic myelogenous leukemia with anemia, thrombocytopenia, hemorrhagic diathesis.
3. Hemoperitoneum, 6000 cc.
4. Lower nephron nephrosis.

SUMMARY OF CASE 185

History: This 57-year-old man entered the hospital for elective definitive surgery for a duodenal ulcer, known to have been present for 5 years.

He had been on medical treatment, the details of which are not available. He gave a history of painless jaundice 5 years before admission, clearing in 1 week, for which he was not studied medically.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 140/80. There was no mass or tenderness in the abdomen.

Clinical Course: After 2 days in the hospital he had an elective operation for a subtotal gastrectomy, gastrojejunostomy, and appendectomy, under spinal and general anesthesia. He did well postoperatively until the 4th day, when he became hypotensive and showed evidence of bleeding through his nasogastric tube. There was good response to transfusion of blood, dextran, and Levophed, and the bleeding apparently stopped.

On the 6th day there was evidence of wound infection and more nasogastric bleeding.

On the 7th postoperative day he was found to have both upper and lower gastrointestinal bleeding and was taken to surgery in shock; a laparotomy was performed under general anesthesia. He was found to have blood in his stomach and in his free peritoneal cavity, although no source for bleeding was found. The procedure consisted of laparotomy, exploratory gastrotomy, and splenectomy, with transfusion of 3500 cc of blood. After this, he was hypotensive in spite of being given blood, Levophed, and dextran; was oliguric; and had poor clearing of his respiratory tract, requiring a tracheostomy, which was done under local anesthesia. He was first noted to be jaundiced 18 hr after the second operation and died 19 hr after the second operation.

Necropsy Findings:

1. Acute hepatic necrosis with jaundice.
2. Hemorrhage into the gastrointestinal tract.
3. Hemoperitoneum, with fibrinous peritonitis.
4. Acute toxic nephrosis.
5. Severe coronary arteriosclerosis.
6. Pulmonary congestion, edema, atelectasis, and pneumonia.

SUMMARY OF CASE 205

History: This 58-year-old man, known to have rheumatoid arthritis, entered the hospital because of fever.

He had had arthritis for at least 3 years, involving his knees and ankles, and had been on adrenal steroids all that time. Nine weeks before admission, he developed increased pain in his back, as well as fever, was hospitalized elsewhere, and was given higher doses of adrenal steroids. One month before this admission, he was hospitalized elsewhere and was started on ACTH, four units/day, which had been continued until the time of admission, and had been given Chloromycetin for 4 days.

Physical Examination: He appeared to be chronically ill, was slightly jaundiced, and was having a shaking chill. He had a maculopapular rash over his face. The liver was palpable two fingerbreadths below the costal margin and there was definite right upper quadrant tenderness.

Clinical Course: In his first 4 days in the hospital, he was studied very extensively, principally for arthritis, jaundice, and high swinging fever, as high as 106 F. On the 5th day he underwent an operation because of the continuing fever, jaundice, development of a liver flap, right upper quadrant tenderness, and a palpable mass that was thought to be the gallbladder. The operation, performed under general anesthesia, consisted of a cholecystectomy, common bile duct exploration, and liver biopsy. There were stones in the gallbladder, but none in the common bile duct. The common bile duct was not dilated or thickened. The liver did not appear normal.

Postoperatively, he did well the first few days, but became disoriented, more deeply jaundiced, confused, and comatose, developed liver flap, passed dark blood through his nasogastric tube, passed practically nothing through his T-tube, and, terminally, became oliguric and developed peripheral edema and pulmonary congestion. He died 8 days after surgery, or 12 days after admission to the hospital. He was hypotensive throughout his entire hospital course, including before, during, and after the operation.

Necropsy Findings:

1. Central lobular necrosis of liver, massive, ? toxic etiology.
2. Fat necrosis of pancreas.
3. Chronic arthritis.
4. Hemorrhage, fresh, moderate, subarachnoid space, left frontotemporal region, Sylvian fissure over left cerebral hemisphere, source undetermined.

SUMMARY OF CASE 222

History: This 44-year-old man entered the hospital for elective cardiac surgery for aortic stenosis.

He had been known to have a heart murmur since the age of 6 and had had easy fatigue all his life, increasing in the past 5 years, and accompanied by dyspnea on exertion. For 2 years he had had substernal pain with exercise, and had taken reserpine, 0.25 mg/day, as an "antithyroid" medication and Preludin, three times a day, for control of weight. He was allergic to sulfas.

He had been in the hospital for 3 days, 4 months before, when cardiac catheterization performed under local anesthesia showed findings compatible with aortic stenosis. Laboratory findings at that time were: hemoglobin, 13.8; PVC, 46.5; WBC, 10,500; urinalysis, normal; BUN, 16; sodium, 139; potassium, 4.5; chloride, 104; CO_2 combining power, 31; calcium, 10.8; phosphorus, 3.7; alkaline phosphatase, 2.2; bilirubin, total 1.4, direct 0.4, and indirect 1.3; BSP retention, 0; prothrombin time, 100 percent; and transaminase, 14. He was discharged with instructions to lose weight, which he did, and then was admitted for elective surgery.

Physical Examination: He was well nourished, had evidence of cardiac enlargement, had a systolic murmur and a probable diastolic murmur, had no jaundice, and had no abdominal mass or tenderness. Blood pressure was 110/68.

Clinical Course: After 5 days in the hospital, he had an aortic valvulotomy and open-heart procedure, under general anesthesia, with unknown drugs, involving a rotating-disk pump oxygenator, with potassium-induced cardiac arrest. At the end of the operation, he had leaking from the aortic suture line, and ventricular fibrillation requiring several drugs and 27 defibrillating shocks. Time on the pump was 68 min. There was considerable bleeding from the chest wall during the closure.

In the recovery room he became jaundiced and then cyanotic, had evidence of continued bleeding from his chest tubes, became hypotensive down to 80/60, and required a considerable amount of blood.

For the first 3 postoperative days, he remained jaundiced and oliguric, with no urine output, and on the 4th day he was dialyzed on an artificial kidney because of his rising serum potassium level. He developed atrial fibrillation, paroxysmal atrial tachycardia, and congestive heart failure, and died 5 days after surgery. He was not hypotensive in the last few days, but remained jaundiced and oliguric.

Necropsy Findings:

1. Rheumatic heart disease with calcific aortic stenosis and cardiac hypertrophy.
2. Acute passive congestion of lungs and spleen.
3. Acute passive congestion of the liver with centrilobular necrosis.
4. Ischemic nephrosis.

SUMMARY OF CASE 223

History: This 55-year-old woman had been known to have an esophageal hiatus hernia for 3 years, manifested by pain after eating, with nausea and vomiting, but never with the vomiting of blood.

Two months before her final hospital admission, she had an exacerbation of her chronic stasis ulcers of her legs and was placed on bedrest with the feet elevated. This made the symptoms of the esophageal hiatus hernia much worse. After 2 months of elevation of the feet she was allowed to walk again; the symptoms of the hiatus hernia were still severe. Accordingly, she was admitted for study.

Twenty years before, she had allegedly suffered lead poisoning by inhaling fumes or dust from painting. This was manifested by the loss of hair and easy bruising, poor healing, and bleeding from minor wounds, which she had allegedly had for 20 years.

She had been on Diamox and Diuril.

Physical Examination: She was obese, pale, and not jaundiced. Blood pressure was 90/55. The abdomen was obese, with no mass or tenderness. There were edema and stasis changes of both legs. The femoral pulses were palpable, but no pulses were palpable distally.

Clinical Course: She was found to be markedly anemic, and was studied very intensively for the cause of the anemia. The only thing that could be proved was an abnormality of thromboplastin generation.

On her 11th day in the hospital, she suddenly developed severe pain, numbness, and coldness and mottling of both lower extremities, was found to have no femoral pulses, and was thought to have thrombosis of the aorta. Accordingly, she underwent an emergency operation in which she was found to have thrombosis of the abdominal aorta, iliac arteries, and left femoral artery; for this she had a Teflon bypass graft from the abdominal aorta to the right common femoral artery. She was incidentally found to have acute cholecystitis with gangrene, and a cholecystostomy was done.

After this, the right leg was warm temporarily, but within 1 day both legs were cold, the pulses had again disappeared, and her urine volume fell to less than 300 cc/day. She never became jaundiced. Details of blood pressure terminally are not known. She died 3 days after surgery, and 14 days after admission to the hospital.

Necropsy Findings:

1. Thrombosis of the abdominal aorta from below the superior mesenteric artery distally, with thrombosis of common iliac and femoral arteries and thrombosis of the right femoral vein and right surgical aorticofemoral prosthesis.
2. Ischemic nephrosis. (There was marked narrowing of both renal artery orifices.)
3. Central zone and confluent necrosis of liver with hepatitis.
4. Thrombosis of the splenic artery with multiple splenic infarcts.
5. Infarction of the gallbladder.
6. Thrombi in pulmonary arteries.
7. Hyperemia and atelectasis of the lungs.
8. Acute and chronic cholecystitis with recent cholecystostomy.
9. Pancreatitis, with fat necrosis.
10. Esophageal hiatus hernia, with gastric hemorrhages.
11. Bilateral adrenal cortical adenomata.
12. Obesity.
13. Multiple cysts of liver.

SUMMARY OF CASE 234

History: This 26-year-old man entered the hospital for elective surgery on the aortic valve and ascending aorta.

He had been known to have Marfan's syndrome for a number of years. Three months before the final hospital admission, he underwent right heart catheterization, and special x-ray studies under local anesthesia showed dilatation of the aortic ring. He had no history of congestive heart failure. He had been on digitalis for 4 months before the final hospital admission.

Physical Examination: He was tall, well developed, and well nourished, with long thin fingers, ectopic lenses, and pectus excavatum. He had the findings of aortic insufficiency and left ventricular hypertrophy. He was not jaundiced and there was no adbominal mass or tenderness. Blood pressure was 140/50 in the left arm and 60/40 in the right arm.

Clinical Course: Three days after admission to the hospital, he underwent resection of the ascending aorta with plastic repair of the aortic valve and excision of one of the three valve leaflets done with total cardiac bypass on a heart-lung machine with hypothermia. The operation lasted 9 hr, with bypass time of 1 hr 36 min, and with a 30-min period of difficulty in restarting the heart.

Postoperatively, he remained hypotensive and intermittently comatose, with changing neurologic signs and with jaundice on the 2nd day. Cyanosis with ecchymosis, edema, ascites, and decerebrate rigidity preceded his death 11 days after surgery, and 14 days after admission to the hospital. During this postoperative period, dehiscense of his chest wound occurred twice, and peritoneal dialysis was performed twice.

Necropsy Findings:

1. Marfan's syndrome, with arachnodactyly, arched palate, bilaterally, subluxated lenses, pes cavus, and hammer toes.

2. Dissecting aneurysm, thoracic and abdominal aorta.
3. Aortic insufficiency.
4. Left ventricular hypertrophy, 790 g.
5. Bilateral hemothorax: left, 800 cc; right, 600 cc.
6. Pulmonary congestion, edema, and hemorrhage, marked.
7. Acute tubular nephrosis ("shock kidneys").
8. Uremic pericarditis, uremic pleuritis, "uremic pancreatitis," and "uremic frost."
9. Centrilobular congestion and necrosis of the liver, marked.
10. Hemorrhagic gastritis.
11. Cerebral hemorrhages, multiple, terminal.

SUMMARY OF CASE 255

History: This 49-year-old woman entered the hospital for elective surgery of lymphosarcoma of the intestines, diagnosed elsewhere.

She had been transiently jaundiced at the age of 9. No other information was available about this episode. She had never been jaundiced at any other time.

Three years before the final hospital admission, she developd abdominal pain and was thought, on the basis of x-rays, to have ulcerative colitis; she improved on medical treatment.

Two months before the final hospital admission she was found, on a routine examination, to have an enlarged uterus. She had an exploratory laparotomy in another hospital, and a bilateral salpingo-oophorectomy and total hysterectomy. The uterus showed myomata and adenosis. During the operation, three "sacculations" were found on the small intestines, and two of these were resected and later found to show lymphosarcoma involving the small intestines. After this, she did well, was discharged, and was readmitted 6 weeks later for elective surgery.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 130/80. The liver was palpable 2 cm below the right costal margin, and the spleen 2 cm below the left costal margin.

Clinical Course: She was studied very carefully in a cancer research institute, and 42 days after admission had her second operation. This was an exploratory laparotomy and biopsy of a mesenteric lymph node, which showed lymphosarcoma. There was involvement of the left lobe of the liver, enlargement of the spleen, and extensive involvement of the mesenteric lymph nodes and the mesentery. No definitive resection was carried out.

Her course after this was uneventful. Nineteen days after surgery, she had chemotherapy with nitrogen mustard, 0.4 mg/kg, for a total dose of 20 mg. She did reasonably well after this, but 4 weeks after surgery gradually developed back pain, jaundice, and confusion, progressing to coma with a liver flap, fever as high as 102 F, gastrointestinal bleeding, hypotension, and death, 35 days after operation, 77 days after admission to the hospital, and 138 days after the original operation and diagnosis of lymphosarcoma.

Necropsy Findings:

1. Malignant lymphoma (lymphosarcoma) with infiltration of stomach, intestines, submaxillary salivary gland, mesenteric lymph nodes, liver, and spleen.
2. Acute massive necrosis of the liver.
3. Cerebral edema.
4. Regurgitation and aspiration of gastric contents.
5. Acute tracheobronchitis.
6. Focal pulmonary edema and hemorrhage.
7. Bile nephrosis.

SUMMARY OF CASE 328

History: This 27-year-old woman was readmitted to the hospital 38 days postpartum because of anorexia, nausea, vomiting, fever, and malaise of 9 days' duration.

During the 26th week of her pregnancy, she had been admitted to the hospital for 4 days for vaginal bleeding, which cleared with no specific measures. She was then re-admitted in the 30th week of pregnancy, i.e., 38 days before the final admission, with a large amount of sudden, painless third-trimester bleeding. She was hypotensive with a pressure of 60/40, and remained so for about 2 hr. Examination showed complete placenta previa, and within 2 hr of admission, an emergency low cervical cesarean section under general anesthesia was performed, in which she was delivered of a 1700-g living child. During the cesarean delivery, which lasted about 45 min, her blood pressure returned promptly with transfusion from 100/60 to 120/80. She received a transfusion of a total of 2000 cc of blood before and during the cesarean delivery. The baby died at the age of 18 hr and autopsy showed prematurity and hyaline membrane disease. In her postoperative course, the mother received Ergotrate, penicillin, streptomycin, Demerol, and 1000 cc of blood, 2 days postpartum. Her postpartum course in the hospital was otherwise uneventful and she was discharged 9 days postpartum with a PCV of 33.

She remained home for 1 month and was essentially well until 5 days before the final admission, when she developed anorexia, nausea, vomiting, fever as high as 105 F, malaise, and dark urine, although she had not noted jaundice. The history was later reviewed in detail with the patient and relatives, and no history of exposure or ingestion of toxins could be uncovered.

Physical Examination: She was severely ill, slightly jaundiced, vomiting, and disoriented. Temperature was 39 C, pulse 112, and blood pressure 100/70. The liver was palpable

two fingerbreadths below the right costal margin and was smooth and moderately or questionably tender.

Clinical Course: In her 2 days in the hospital, she became more irritable, disoriented, and more deeply jaundiced, and developed ecchymosis, first over her legs and then all of her body. She then developed decerebrate rigidity. Bleeding was seen from intravenous infusion sites, and a tracheostomy was performed under local anesthesia, with some difficulty caused by oozing of blood at the incision. A lumbar puncture was negative. Her urine output diminished to 600 cc per 24 hr. She died 2 days after admission to the hospital, and 40 days after the cesarean section.

Necropsy Findings (coroner's necropsy):

1. Massive necrosis of liver.
2. Hypostatic congestion and edema of the lungs.
3. Toxic nephrosis.
4. Multiple ecchymoses.
5. Cerebral edema.

SUMMARY OF CASE 338

History: This 14-year-old white girl entered the hospital for elective cardiac surgery.

She had been known to have congenital heart disease since birth, and had always had dyspnea on exertion, decreased exercise tolerance, cyanosis with exercise, and frequent upper respiratory infections.

One month before, she had been admitted for cardiac catheterization and cineangiograms, which showed interventricular septal defect and infundibular stenosis.

She had never been jaundiced and was on no medications.

Physical Examination: She was well developed, cyanotic, and not jaundiced. Blood pressure was 110/60. The heart was not enlarged but had a systolic murmur. The liver was not palpable.

Clinical Course: Two days after admission, she underwent a procedure for closure of an interventricular septal defect, resection of infundibular stenosis, and tracheostomy under total cardiopulmonary bypass on a heart-lung machine with hypothermia.

She tolerated this procedure and was doing well until the 8th day, when she abruptly became febrile and hypotensive, and was thought to have pulmonary embolism or septicemia. She was treated with blood, antibiotics, and steroids, became anuric, never became jaundiced, but died 9 days after surgery, and 11 days after admission to the hospital.

Necropsy Findings:

1. Tetralogy of Fallot.
2. Multiple foci of acute myocardial necrosis.
3. Severe acute and chronic passive congestion and edema and hemorrhage in both lungs.
4. Diffuse interstitial pneumonia.
5. Atelectasis of lower lobes.
6. Acute passive congestion of viscera.
7. Massive acute central necrosis of liver cells.
8. Ascites.
9. Bilateral pleural effusion.

SUMMARY OF CASE 345

History: This 34-year-old police officer entered the hospital with a history that shortly before admission he had suddenly become delirious, with marked confusion, belligerent behavior, and thrashing about, possibly moving the right upper and lower extremities more than the left. There was a history of heavy alcoholic intake, but further details were not available.

Physical Examination: He was belligerent, uncooperative, and complaining of headache, and had a stiff neck. Blood pressure was 145/80. He was not jaundiced, and there was no abdominal mass or tenderness. He had bilateral positive Babinski sign.

Clinical Course: Lumbar puncture showed bloody spinal fluid under increased pressure. A right carotid arteriogram performed under local anesthesia showed an aneurysm at the bifurcation of the right internal carotid artery into the anterior and middle cerebral arteries.

Two days after admission, he had a right frontotemporal craniotomy, under hypothermia, with clipping of the aneurysm. This involved 28 min of clamping temporarily of the internal carotid artery. After this operation he did well, except for slight weakness on the left side. Nine days after surgery he became confused, with left homonymous hemianopsia, with increasing weakness on the left. A second right carotid arteriogram showed a shift in the right anterior and middle cerebral artery, and pneumoencephalogram showed a mass, or swelling, in the left posterior temporal region.

Accordingly, 11 days after operation 1, he underwent operation 2, which was a repeat craniotomy in which swelling, but no other specific finding, was found. After the second operation, he was confused and still weak on the left side, and developed seizures on the left; 6 days after operation 2, he became hypotensive, to the level of 80/60, and jaundiced. The jaundice was thought to be on the basis of hemolysis. He was given blood and hydrocortisone, but died 1 day after the onset of jaundice, 7 days after operation 2, 18 days after operation 1, and 19 days after admission to the hospital.

Necropsy Findings:

1. Encephalomalacia at the base of the right temporal lobe, 4 x 6 cm.

2. Pulmonary edema and congestion, acute.
3. Fatty infiltration and necrosis of the liver.
4. Extradural hematoma in the right frontotemporal area, 10 cc.
5. Recent hemorrhage in atheromatous plaque of the wall of the right middle cerebral artery.

SUMMARY OF CASE 352

History: This 75-year-old white man, who was an active working farmer, was admitted with a small bowel obstruction, as a transfer from another hospital.

Twenty-four years before, he had had an operation elsewhere for a small bowel obstruction due to adhesions. Twenty years before, he had had another operation for a strangulated femoral hernia.

Three weeks before the final hospital admission, cramping abdominal pain developed and a week later, he was admitted to another hospital at which he received unknown medications and from which there is no information as to what was done, except that no surgery was performed. Four days before the final transfer, he developed vomiting and abdominal distention and was found to have bowel obstruction. He had never been jaundiced.

Physical Examination: He was thin, acutely ill, and dehydrated, but not jaundiced. Blood pressure was 150/90. The abdomen was distended and tender, without rigidity or mass. Bowel sounds were hyperactive.

Clinical Course: He was treated with a Cantor small intestinal tube for 2 days with replacement of fluids and electrolytes and with blood and antibiotics, but without improvement of his small bowel obstruction.

Two days after admission, an exploratory laparotomy was performed, with divisions of adhesions and repair of an accidental perforation of the small intestine. There was considerable contamination of the peritoneal cavity with intestinal contents.

After surgery he was always hypotensive and most of the time was cyanotic with rapid respirations, poor cough, inability to clear secretions, and temperature as high as 105 F. He became jaundiced after surgery shortly before death. He died 1 day after surgery, 3 days after admission to the hospital.

Necropsy Findings:

1. Generalized peritonitis secondary to perforation of ileum (repair of ileum intact at autopsy).
2. Moderately severe hepatitis (possibly infectious) with mild jaundice.
3. Pulmonary emphysema with bronchopneumonia.

SUMMARY OF CASE 363

History: This 51-year-old man entered the hospital with a 4-month history of weakness, 20-lb weight loss, diarrhea of eight watery stools per day, anorexia, dark urine, and light stools.

He had a 1-month history of progressive abdominal enlargement and jaundice. He had been taking unknown shots and pills in a doctor's office for 4 months. He had been an alcoholic for 20 years, but allegedly had had no alcohol for 5 months. No further information is available as to the amount of alcohol.

Physical Examination: He was thin and deeply jaundiced. The abdomen was markedly distended with ascites; there was vague right upper quadrant tenderness, but no mass. Blood pressure was 120/70.

Clinical Course: X-rays showed complete pyloric obstruction. In his first few days in the hospital, he did poorly, continued to vomit, had slight blood tinging of the vomitus, and had paracentesis of 500 cc of fluid, which showed Class III cells on cytologic examination.

Five days after his admission, an exploratory laparotomy was performed and he was found to have carcinoma of the pancreas, with metastasis to the peritoneum, small intestine, diaphragm, and liver, and with obstruction of the common duct up to the cystic duct. The procedure consisted of a palliative gastrojejunostomy and choledochojejunostomy.

After this operation he became confused, had marked fluid and electrolyte imbalance, gradually deteriorated, remained jaundiced, and died 4 days after surgery, and 9 days after admission to the hospital.

Necropsy Findings:

1. Adenocarcinoma of the head of the pancreas, undifferentiated, with metastasis to peritoneum, liver, diaphragm, lungs, adrenals, small intestine, and muscle.
2. Obstructive jaundice.
3. Ascending cholangitis and hepatitis.
4. Bile nephrosis.
5. Gastric dilatation, marked. (Stomach extended down to the pelvis at necropsy.)
6. Pulmonary edema.
7. Pulmonary infarction, recent.
8. Bilateral pleural effusion.

SUMMARY OF CASE 605

History: This 59-year-old white man, a merchant seaman, entered the hospital because of coughing up blood.

Two years before the final hospital admission he had had a gastrectomy for carcinoma of the stomach, which was said to be a "carcinoma simplex," localized to the pylorus of the stomach and adherent to the gallbladder.

He had been on Thorazine, 25 mg four times a day, for 2 years before the final hospital admittance, for nervousness. Alcoholism was denied.

Physical Examination: He was poorly nourished and appeared chronically ill. He was not jaundiced. Blood pressure was 120/80. There was no abdominal mass or tenderness.

Clinical Course: An x-ray and sputum examination showed far-advanced pulmonary tuberculosis with cavitation, and for this he was treated with drugs and remained in the hospital for a total of 3 years 7 months. His sputum became negative.

Two months before death he became jaundiced for the first time, and developed epigastric tenderness, dark urine, light stools, and enlargement of the liver to five to six fingerbreadths below the right costal margin. All of the time in the hospital he had been on Thorazine, 10 mg three times a day. The jaundice was thought to be due to the Thorazine.

He was studied and observed for the jaundice for 47 days and finally underwent an exploratory laparotomy, cholecystectomy, common bile duct exploration, and liver biopsy. The common bile duct was thickened, but no stone was found. Microscopic examination was interpreted as showing metastasis of the carcinoma from the stomach to the gallbladder. No other evidence of carcinoma was found. The liver biopsy showed necrosis, acute inflammation, and biliary stasis.

After the operation, he became more deeply jaundiced, vomited blood, was given blood by transfusion, was hypotensive the last 3 days of life, and died 9 days after surgery, 2 months after the onset of jaundice, and 3 years 7 months after admission to the hospital.

Necropsy Findings:

1. Carcinoma of the stomach, 5 years after subtotal gastrectomy, infiltrating and undifferentiated (by history).
2. Periportal metastases (by surgical specimen).
3. Obstructive jaundice.
4. Bile nephrosis.
5. Acute necrosis of the liver.
6. Generalized peritonitis.
7. Chronic gastritis with ulceration and gastrointestinal bleeding.

SUMMARY OF CASE 609

History: This 13-year-old white girl entered the hospital for elective surgery for interatrial septal defect.

She had been known to have a heart murmur since the age of 5 months. She had had cardiac catheterization at the age of 3 years, and had been found to have a septal defect. She had never had symptoms of cardiac disease and had never been jaundiced.

Two months before the final hospitalization, she had been admitted for 2 days for cardiac catheterization, which had shown findings of an interatrial septal defect. She had received penicillin and other injections at that time.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 130/80. There were diastolic and systolic murmurs along the left sternal border. There was no abdominal mass or tenderness.

Clinical Course: Two days after her admission to the hospital she had repair of the interatrial septal defect under hypothermia, with total cardiopulmonary bypass on a heart-lung machine. During this procedure, she had ventricular fibrillation during most of the repair. On the 1st day she was transiently hypotensive to 60/40. On the 2nd day she started to have convulsions, originating in the left upper extremity. After 1.5 hr of this, she had cardiac arrest from which she could not be resuscitated. Details of urine volume are not clear. She was never jaundiced. She died 2 days after surgery and 4 days after admission to the hospital.

Necropsy Findings:

1. Interatrial septal defect, repaired.
2. Pulmonary edema.
3. Hemorrhagic centrilobular necrosis of the liver.
4. Acute tubular necrosis of the kidneys.

Comment by Pathologist: "Death in this patient cannot be adequately explained on the basis of the anatomic findings."

SUMMARY OF CASE 616

History: This 81-year-old white man entered the hospital shortly after a fall because of a fractured hip.

Only a vague history was available that he had been markedly short of breath for at least 5 years.

Physical Examination: He was confused, cyanotic, dyspneic, and unable to give a history. He was judged to be in critical condition. He was not jaundiced. Blood pressure was 70/40, pulse was 120, and respiration was 42. He appeared to be in marked respiratory distress and insufficiency, with diffuse wheezes, rales, and rhonchi. There were signs of cardiac enlargement. The abdomen was distended, but there was no abdominal mass.

Clinical Course: He was treated very intensively on a medical ward for 10 days before the surgery for his fractured hip. He had ileus, which was treated with a nasogastric tube that returned material with traces of blood in it. He had severe chronic bronchitis with obstructive emphysema,

and for this he was treated with a respirator for 10 hr and then numerous medical measures. He had urinary retention, treated with a catheter. He had hypotension, treated with a Neo-synephrine drip.

Ten days after admission, he had placement of a prosthesis in his left hip. Following this, he gradually improved and by the 9th day was ready to be discharged, when he suddenly began vomiting blood. He was hypotensive and bleeding failed to be stopped with conservative measures.

Ten days after the first operation and 20 days after admission, he underwent a second procedure, which included esophagoscopy, 50 percent subtotal gastrectomy, vagotomy, gastroduodenostomy, liver biopsy, and tracheostomy. After this procedure, he never did well. From the 1st day onward he was hypotensive and dependent on a vasopressor. He bled from around his tracheostomy, passed dark bloody material by rectum, became oliguric, gradually deteriorated, was never jaundiced, and died 3 days after operation 2, 13 days after operation 1, and 23 days after admission to the hospital.

Necropsy Findings:

1. Final necropsy summary and microscopic reports not available.
2. Pulmonary emphysema, bilateral, marked, with extensive bleb formation.
3. Pulmonary congestion and edema, bilateral, marked.
4. Acute tracheobronchitis.

SUMMARY OF CASE 618

History: This 5-year-old girl entered the hospital 3 hr after a massive abdominal injury. She had been climbing on a 100-gal weed-spraying tank with her brother and the tank fell on the two of them. She was hospitalized elsewhere and received 1000 cc of blood. No other information is available as to what happened in the other hospital. She arrived at the final hospital 3 hr after the injury.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 110. She was in severe abdominal pain. There was diffuse abdominal tenderness and guarding.

Clinical Course: Two hours after admission, she was taken to surgery and underwent an exploratory laparotomy through an abdominal incision. She was found to have multiple extensive lacerations of the liver, and the procedures included an attempted repair of the lacerations and suturing of omentum into the largest of the lacerations. Abdominal drains and a chest tube were placed.

After surgery she was variably hypotensive from 0 to 80, but was doing reasonably well with blood and vasopressors. She was never jaundiced. She died unexpectedly 2 days after surgery and admission to the hospital.

Necropsy Findings:

1. Fracture of the right lobe of the liver.
2. Extensive necrosis (Grade 3) of the liver, with insufficiency central necrosis.
3. Collapse of the lower and middle lobes of the right lung with alveolar hemorrhage.
4. Cerebral edema.

SUMMARY OF CASE 619

History: This 13-year-old girl entered the hospital for elective cardiac surgery.

A heart murmur had first been discovered when the patient was 7 years old. For 2 years, the patient had had gradually increasing easy fatigue, dyspnea on exertion, and cyanosis with exertion.

She had been studied at another hospital approximately 1 year before and the diagnoses established had been: ventricular septal defect with left-to-right shunt, and pulmonary hypertension, but there was some uncertainty about this.

Physical Examination: The child was well nourished, not cyanotic, and not jaundiced. Blood pressure was 114/50. There was a systolic murmur. There was no abdominal mass or tenderness.

Clinical Course: She was thought to have ventricular septal defect with left-to-right shunt and pulmonary hypertension. One day after admission, she underwent a complex cardiac operation with total cardiopulmonary bypass on a heart-lung machine, and was found to have a very unusual condition involving a patent ductus arteriosus, a congenital deformity of the mitral valve, an extremely large interventricular septal defect, anomalous tricuspid valves, and severe pulmonary hypertension. The procedures included ligation of the patent ductus arteriosus, partial repair of the ventricular septal defect with a Teflon prosthesis, and attempted correction of the mitral valve deformity. It was felt that identification of the structures was not accurate and that the repair was unsatisfactory.

After surgery, the patient was hypotensive, gradually deteriorated, was thought to have mitral and tricuspid insufficiency, and became oliguric but never jaundiced. She died 19 hr after surgery, and 2 days after admission to the hospital.

Necropsy Findings:

1. Anomalous position of atrial septum with communication of right atrium with both ventricles and communication of left atrium with left ventricle through accessory mitral orifice.
2. Pulmonary edema.
3. Central necrosis of the liver.

SUMMARY OF CASE 620

History: This 6-year-old girl entered the hospital for elective cardiac surgery for known tetralogy of Fallot.

She had been known to have congenital heart disease since the age of 5 months, when she became cyanotic with a respiratory infection. She had had gradually increasing cyanosis over the years, especially with crying and exertion. She had progressive fatigue and dyspnea with exertion, and limited physical activity and physical and mental development. She had been on oral penicillin. It is not known whether she had had cardiac catheterization. It is likely that this was performed elsewhere.

Physical Examination: She was well nourished, small, moderately cyanotic, and not jaundiced. Blood pressure was 100/60. There was a systolic murmur and clubbing of the extremities.

Clinical Course: One day after admission she underwent open-heart surgery, consisting of repair of the ventricular and atrial septal defect with reconstruction of a right ventricular outflow tract with a Teflon prosthesis. This was done with total cardiopulmonary bypass and a heart-lung machine with intentional hypothermia. She was in poor condition from the end of the operation onward, with severe hypotension in spite of large doses of vasopressors. She also had cyanosis and atrioventricular dissociation. Her urine volume fell to 175 cc/day. Terminally she developed congestive heart failure with enlargement of the liver. She was never jaundiced, but died 4 days after surgery, and 5 days after admission to the hospital.

Necropsy Findings:

1. Congestion and edema of the lung with hemorrhages.
2. Congestion and hemorrhage of Peyer's patches of the small intestine.
3. Right aortic arch.
4. Peripheral congestion of liver with central lobular necrosis.
5. Terminal aspiration of gastric contents.
6. Tetralogy of Fallot, repaired.

SUMMARY OF CASE 628

History: This 6-year-old white boy entered the hospital for elective cardiac surgery for known congenital heart disease.

He had been known to have heart disease since the age of 1 month, and had been cyanotic with eating and playing.

At the age of 3 years, cardiac catheterization and cardiac surgery were performed elsewhere. That was 3 years before the final hospital admission. At this procedure, he underwent dilatation of congenital pulmonic stenosis, and after this was less cyanotic but still had dyspnea on exertion.

Physical Examination: He was well nourished and not jaundiced, but moderately cyanotic. Blood pressure was 90. There was a loud systolic murmur. No abdominal mass or tenderness was noted. There was clubbing of the extremities.

Clinical Course: Cardiac catheterization under local anesthesia was performed, showing tetralogy of Fallot with infundibular and valvular stenosis, ventricular septal defect, and hypoplasia of the pulmonary artery.

Seventeen days after admission, he underwent open-heart surgery, consisting of repair of the ventricular septal defect and reconstruction of the right ventricular outflow tract under total cardiopulmonary bypass on a heart-lung machine with hypothermia.

After surgery, his temperature rose to 104 F, his blood pressure fell to 0, and his pulse rate increased. He remained cyanotic, had a satisfactory urinary output, and never became jaundiced, but died 19 hr after surgery, and 18 days after admission to the hospital.

Necropsy Findings:

1. Tetralogy of Fallot, operated.
2. Mediastinal hematoma, 200 cc.
3. Right-sided aortic arch.
4. Acute central necrosis of the liver.

SUMMARY OF CASE 632

History: This 10-year-old girl entered the hospital for elective cardiac surgery.

She had been known to have a heart murmur since the age of 3 years.

Nineteen months before final hospitalization, cardiac catheterization was performed elsewhere, and she was found to have a ventricular septal defect, patent ductus arteriosus, patent foramen ovale, and pulmonary hypertension with bidirectional shunt.

A procedure for closure of the patent ductus arteriosus was performed under general anesthesia 1 year before the final hospital admission. Two weeks later, she again had cardiac catheterization, showing a pulmonary-to-systemic flow ratio of 1.3 and persisting severe pulmonary hypertension. She was rarely cyanotic.

Physical Examination: She was tall, thin, and not jaundiced, but slightly cyanotic. Blood pressure was 95/70. There were systolic and diastolic murmurs. There was no abdominal mass or tenderness.

Clinical Course: She again underwent cardiac catheterization, which showed a ventricular septal defect with a bidirectional shunt and pulmonary hypertension.

Three days after admission she underwent repair of the ventricular septal defect on a heart-lung machine. This operation was done with considerable difficulty; afterward, her condition remained unsatisfactory, with cyanosis, respiratory stress, and unstable blood pressure. A tracheostomy was performed under local anesthesia, but she died 2 days after surgery, and 5 days

after admission to the hospital. She was never jaundiced.

Necropsy Findings:

1. Plexiform change (endothelial proliferation) of pulmonary arteries, severe.
2. Edema of lower lobes of both lungs.
3. Residual (4 mm) ventricular septal defect.
4. Atrial septal defect.
5. Pulmonary arteriosclerosis.
6. Central necrosis of liver, lobular.

SUMMARY OF CASE 636

History: This 55-year-old man entered the hospital for elective cardiac surgery.

At the age of 12 years, he had had rheumatic fever, and had been known to have a heart murmur since the age of 34.

For 12 years, he had been known to have aortic stenosis, but this had not produced symptoms.

In recent years, a gradual increase in fatigue and dyspnea on exertion was noted, and he developed left ventricular hypertrophy on his electrocardiogram and cardiac enlargement on his chest x-ray.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 90/70. There was a characteristic murmur of aortic stenosis, but no abdominal mass or tenderness.

Clinical Course: Measurement of left ventricular and aortic pressure under local anesthesia showed a marked gradient across the aortic valve.

Two days after admission open-heart surgery was performed, consisting of resection of the heavily calcified aortic valve on a heart-lung machine. This was complicated by a fracture of the aortic wall with massive hemorrhage but eventual repair.

After surgery there was considerable bleeding, and he was suspected of having cardiac tamponade. He was returned to surgery 7 hr after the first operation for reopening of the thoracotomy with attempted control of hemorrhage. No distinct bleeding point was found, only diffuse bleeding.

After the second operation, he remained hypotensive in spite of Adrenalin drip, became oliguric to 70 cc/day, and had a tracheostomy. He was never jaundiced, but died 3 days after operations 1 and 2, and 5 days after admission to the hospital.

Necropsy Findings:

1. Residual diffuse mediastinal hemorrhage.
2. Acute anterior myocardial infarction.
3. Acute dissecting aneurysm, origin left iliac artery, extending to the root of the aorta.
4. Bilateral hemorrhagic pulmonary edema with atelectasis.
5. Acute lower nephron nephrosis, with renal insufficiency.
6. Cerebral edema.
7. Infarct of the liver.
8. Acute central passive congestion of the liver with central necrosis.

SUMMARY OF CASE 645

History: This 44-year-old white man entered the hospital for the seventh time because of increasing shortness of breath and debility.

He had been followed for 2 years with chronic congestive heart failure, the etiology of which had never been clear. He had been thought possibly to have hypertensive cardiovascular disease, because of some mild hypertension in the past, or, more recently and more likely, idiopathic myocarditis, and had been treated with sodium restriction and multiple drugs.

Multiple pulmonary emboli were also noted, with the source not definitely known, and he was hospitalized for 1 week (and discharged 1 week before the final hospitalization) for another episode of probable pulmonary embolism.

Digitalis, Coumadin, iron, and morphine with Mercuhydrin by injection were the medications used.

He had never been jaundiced.

Physical Examination: He was thin, chronically ill, and not jaundiced. His respiration was irregular and he had a temperature of 39 C, pulse of 140, and blood pressure of 88. He was thought to be questionably jaundiced by only one observer. There was venous distention in the neck. The heart was enlarged to the midaxillary line and had a systolic murmur. The liver was palpable five fingerbreadths below the right costal margin and was tender. There was edema of the feet and ankles, and a questionably tender palpable vein in the right thigh.

Clinical Course: He was treated medically for his chronic congestive heart failure, but continued to have chest pain, hemoptysis, and dyspnea even at rest, and developed friction rubs over both lungs. He gradually deteriorated.

On the 14th day icteric serum was noted, although the patient was never again described as jaundiced. He was thought to have congestive heart failure on an unknown basis with recurrent pulmonary emboli from an unknown souce.

Nineteen days after admission he underwent ligation of the inferior vena cava and after this he remained agitated, drowsy, and confused and was thought to have cerebral anoxia. One more time the serum was described as jaundiced, although the patient was not. In spite of intensive medical management, he continued to do poorly, was never definitely jaundiced, and died 8 days after surgery, and 27 days after admission to the hospital.

Necropsy Findings:

1. Diffuse myocarditis of unknown cause.
2. Extreme cardiac hypertrophy (800 g) with dilatation.
3. Thrombosis of right leg.
4. Pulmonary infarction.
5. Pulmonary congestion, emphysema, atelectasis, and hemosiderosis.
6. Chronic gastric ulcer.
7. Congestion of the liver and other organs.

SUMMARY OF CASE 649

History: This 65-year-old white man entered the hospital for evaluation of an aneurysm of the abdominal aorta and hypertensive cardiovascular disease.

For 4 years before, he had been known to be hypertensive, and had been treated with diet. During this time he had been known to have widening of the abdominal aorta.

He had had intermittent claudication for 2 years and this had increased in severity recently, so that he had claudication with one block of walking.

He admitted using a half-pint of whiskey per day for an unknown period. He was not and had never been jaundiced.

Physical Examination: He was obese and not jaundiced. Blood pressure was 180/90. The liver was palpable two fingerbreadths below the right costal margin. There was a pulsating 8-cm aneurysm of the abdominal aorta. Femoral pulses were palpable, but the pulses in the feet were decreased.

Clinical Course: He was studied in the hospital for 7 days before surgery. Seven days after admission, he underwent resection of an aneurysm of the abdominal aorta with placement of a Dacron Y-graft from the aorta to the iliac arteries and additional placement of two separate Dacron grafts from the Y-graft to the femoral arteries below. The procedure included bilateral lumbar sympathectomy.

Immediately after this operation, his left leg was cold, so he was returned to surgery 2 hr later and underwent a left popliteal thromboendarterectomy.

After the second operation, his condition was satisfactory until the 2nd day, when he became hypotensive to unknown levels. He became oliguric and cyanotic, and his feet became cool and blue. He never became jaundiced, but died 3 days after operations 1 and 2, and 10 days after admission to the hospital.

Necropsy Findings:

1. Bronchopneumonia, early, lower lobe.
2. Infarcts of ileum, colon, kidney, prostate.
3. Pulmonary embolus.
4. Tracheobronchitis.
5. Central congestion with focal liver cell necrosis.

SUMMARY OF CASE 650

History: This 56-year-old white man entered the hospital for the fifth time with the complaint of trouble in swallowing for 3 weeks.

Two years before the final admission, he had had carcinoma of the mouth, treated by a left radical neck dissection, with resection of the left half of the mandible, left half of the floor of the mouth, and a hemiglossectomy. Some 18 months before the final admission, he underwent a right radical neck dissection in which one lymph node was found to be positive. (All lymph nodes were negative in the first operation.)

Some 14 months before the final admission, he developed a left pneumothorax and was found to have malignant cells in his pleural fluid.

Six weeks before final hospital admission, a retrocardiac mass was found on x-ray. At this time he refused surgery and was started on radiation therapy.

He was readmitted finally because of increasing trouble in swallowing. He had never been jaundiced.

Physical Examination: He was thin and not jaundiced. Blood pressure was 130/80. There was evidence of a hemimandibulectomy and bilateral radical neck dissection. One firm lymph node was palpable in the right side of the neck. There was no abdominal mass or tenderness.

Clinical Course: Chest x-ray and esophogram confirmed the presence of a large retrocardiac mass, presumably a metastatic tumor. Six days after admission, an esophagoscopy under local anesthesia was unsuccessful. From the 10th day onward, he had fever to 40 C. On the 13th day a gastrostomy was done under local anesthesia, but later leakage developed around the gastrostomy with continued fever. He produced copious amounts of sputum. X-ray showed leakage of dye from the esophagus into the mediastinal cavity and right middle lobe pneumonia. A tracheostomy was performed under local anesthesia and he remained on intravenous fluid, but deteriorated. Thirty-seven days after admission, he underwent an exploratory thoracotomy, and was found to have a tumor mass in the posterior mediastinum with a fistula involving the esophagus and bronchus. A biopsy was taken and the operable fields were drained.

After this he gradually deteriorated, became pale, weak, increasingly jaundiced, and comatose. He died 19 days after surgery, and 56 days after admission to the hospital.

Necropsy Findings:

1. Metastatic epidermoid carcinoma involving the left posterior mediastinum, the posterior pericardium, myocardium, left atrium, and esophagus.
2. Left posterior mediastinal tumor abscess cavity with openings into esophagus.

3. Acute mediastinitis.
4. Acute bronchopneumonia.
5. Empyema, right and left.
6. Acute suppurative pericarditis with extension into wall of left atrium.

SUMMARY OF CASE 651

History: This 72-year-old white woman entered the hospital for the second time because of jaundice of 6 days' duration.

Some 21 months before, at another hospital, she had been found to have carcinoma of the cervix, Stage III, and had external radiation and then radium implantation twice, for a total dose of 7500 mg-hr. After this, the cervix appeared to heal but the pelvic mass became no smaller. Fifteen months before final hospitalization, she developed low back pain and constipation.

Because of a pelvic mass developing 12 months before final hospitalization, she was admitted into the hospital and was found to have a PCV of 33, hemoglobin of 10.9, bilirubin of 0.3, and BSP retention of 27 percent. She was treated with three units of blood, then injection of 15 cc of Coxsackie B-3 virus directly into the tumor, with no improvement. After this, an anterior pelvic exenteration with creation of ileal bladder was done, and a large pyometra was found, but no tumor. During this operation, a large amount of bleeding occurred, necessitating 18 units of blood. The liver was described as "firm, shrunken, cirrhotic" during this surgery.

On the day of surgery, she became jaundiced for the first time. (It is not clearly stated whether the jaundice was noted before or after surgery.) Bilirubin rose to 4.5 total, with a direct of 4.0 and indirect of 0.5. Her jaundice decreased gradually over a period of 3 weeks. On development of an anti-P factor, this was thought to be evidence of a possible incompatible transfusion. She was discharged after 3 months with liver chemistries still abnormal. At discharge, the alkaline phosphatase was 17.7, bilirubin was 3.0 direct and 1.5 indirect, thymol turbidity was "slowly rising," and serum protein was "inverted."

She was followed in a clinic for 9 months and had progressive worsening of the liver chemistries, with increases in the transaminase, cephalin flocculation, thymol turbidity, and alkaline phosphatase. The BSP retention rose to 52 percent, "chemical, but not clinical jaundice" appeared, and she continued to have a poor appetite, poor food intake, and nausea.

She was admitted finally with weakness, as always, but with 6 days of jaundice without itching.

There was no history of alcoholism, malaria, previous episodes of jaundice, hepatitis, exposure to hepatitis, exposure to hepatotoxin, or use of chlorpromazine or other drugs. She was a Seventh-Day Adventist, used no meat, and was considered to have a very low protein intake.

Physical Examination: The patient was well nourished, weak, drowsy, dehydrated, and very deeply jaundiced. Blood pressure was 110/60. There were no scratch marks, no telangiectases, and no other stigmata of cirrhosis. The liver was "questionably palpable at the right costal margin" and was not tender. The spleen was not palpable. There was a functioning ileal bladder.

Clinical Course: She was studied for several days in the hospital and showed increased drowsiness and increasing jaundice. Laennec's cirrhosis plus acute diffuse hepatic necrosis of unknown etiology was a preoperative diagnosis, but she was considered also possibly to have obstructive jaundice due to metastatic nodes or carcinoma of the head of the pancreas.

Nine days after admission, surgery was done, consisting of an exploratory laparotomy, common bile duct exploration, and cholecystostomy. No biliary tract obstruction was found. The liver was described as "cirrhotic." A T-tube was left in the common bile duct. Nothing definitive was done.

After this operation, she remained deeply jaundiced and comatose, gradually deteriorated, and died 11 days after admission to the hospital, and 2 days after surgery.

Necropsy Findings:

1. Portal cirrhosis, liver.
2. Focal necrosis, liver.
3. Acute and chronic inflammation, portal area, liver.
4. Subacute cholecystitis with cholelithiasis (single small stone found in the gallbladder).
5. Focal acute interstitial pancreatitis.
6. Focal encephalomyelitis.
7. Acute and chronic pyelonephritis, right.
8. Generalized congestion.

Comments by Pathologist: "At necropsy, the findings in the liver were consistent with an acute viral hepatitis, rather than toxic hepatitis, with hepatic necrosis. Mild encephalitis has been reported in instances of viral hepatitis."

SUMMARY OF CASE 653

History: This 24-year-old woman entered the hospital for elective cardiac surgery.

She had been known to be cyanotic and have a heart murmur since birth. No symptoms of congestive heart failure, easy fatigue, or other heart symptoms were known.

Six years before the final admission, she underwent cardiac catheterization elsewhere, showing a ventricular septal defect with a left-to-right shunt and pulmonary hypertension.

One month before the final hospital admission, cardiac catheterization under local anesthesia was performed. This demonstrated a left-to-right shunt, with the right ventricle as the

common recipient chamber and with an anomalous coronary arterial circulation and marked pulmonary hypertension. She had never been jaundiced.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 120/80. There were signs of cardiac enlargement, systolic and diastolic heart murmurs, and a thrill. There was no abdominal mass or tenderness.

Clinical Course: Three days after admission she underwent closure of two interventricular septal defects on total cardiopulmonary bypass with a heart-lung machine. The first defect was repaired with a patch. After she was taken off bypass, a residual shunt was found and she was again placed on bypass for repair of the second shunt.

After this she was in complete heart block, required an internal and then an external pacemaker, became hypotensive, comatose, and oliguric, developed increasing respiratory distress, had a tracheostomy, required increasing doses of vasopressors, was replaced on partial bypass, was never jaundiced, but died 54 hr after surgery and 5 days after admission to the hospital.

Necropsy Findings:

1. Congenital heart disease with two ventricular septal defects, origin of both great vessels from the right ventricle, subaortic stenosis, stenosis of the right pulmonary artery, patent foramen ovale, cardiac hypertrophy.
2. Pulmonary congestion, acute and chronic.
3. Pulmonary edema, moderate.
4. Passive congestion of the liver, acute and chronic with central necrosis (lobular).
5. Petechial hemorrhages in brain with focal hemorrhages in lungs, liver, adrenal, bladder, and rectum.
6. Hemorrhage, acute, anterior mediastinum and right pleural space, 160 g.
7. Pulmonary arterial sclerosis, severe.

SUMMARY OF CASE 657

History: This 10-year-old girl entered the hospital for elective cardiac surgery.

She had been cyanotic since the age of 7 months, and had had cardiac catheterization then, giving a diagnosis of tetralogy of Fallot.

For 2 years before the final hospitalization, she had increasing cyanosis and fatigue with exertion.

She had had cardiac catheterization with angiocardiography 2 weeks before under local anesthesia, confirming the diagnosis of tetralogy of Fallot.

Physical Examination: The patient was small, cyanotic, and not jaundiced. Blood pressure was 90/65. A systolic murmur was heard. No abdominal mass or tenderness was found.

Clinical Course: One day after admission, she underwent repair of the interventricular septal defect and plastic enlargement of the right ventricular outflow tract under total cardiopulmonary bypass on the heart-lung machine. The surgery was inadequate, in that the right ventricular outflow tract could not be enlarged. At the end of the operation, she was dependent on a pacemaker because of complete heart block. After surgery, she was always hypotensive, was never jaundiced, and died 1 day after surgery, and 2 days after admission to the hospital.

Necropsy Findings:

1. Congenital heart disease (tetralogy of Fallot) with intravascular web formation, with relative stenosis, right and left pulmonary arteries, immediately distal to bifurcation.
2. Hemorrhage, anterior mediastinum, lungs, ovaries, small and large intestines, thymus gland, and bone marrow.
3. Fibrinous pericarditis and epicarditis.
4. Pulmonary congestion, marked.
5. Acute massive congestion with central lobular degeneration of the liver.

SUMMARY OF CASE 658

History: This 34-year-old man entered the hospital for evaluation for possible cardiac surgery.

He had rheumatic fever at the age of 9 and subacute bacterial endocarditis at the age of 18.

He was admitted to the same institution 11 months before, was studied, and was found to have marked cardiac enlargement with enlargement of the left atrium and right ventricle and calcification of the mitral valve. Cardiac catheterizaton showed "gross mitral insufficiency." Laboratory findings at that time included: transaminase, 57; BSP, 22 percent; alkaline phosphatase, 13; and bilirubin, 2.3. A diagnosis of mitral insufficiency and right-sided cardiac failure was made.

In the year before the final admission, hospitalization was necessary for several episodes of severe congestive heart failure. He had progressive dyspnea on exertion, orthopnea, peripheral edema, and persistent right upper quadrant pain, thought to be related to the enlarged liver. Treatment including the following drugs: Aldactone, digitalis, Diamox, and Mercuhydrin intramuscularly twice a week.

Intermittent jaundice for the preceding 10 years was thought to be related to right-sided cardiac failure.

Physical Examination: He was chronically ill, thin, and jaundiced. Blood pressure was 106/68, with atrial fibrillation, marked venous distention, edema, and cardiac enlargement. Systolic and diastolic heart murmurs were heard. The liver was enlarged, firm, pulsatile, and moderately tender, extending 11 to 15 cm below the right costal margin. The spleen was palpable two finger-breadths below the left costal margin.

Clinical Course: Intensive medical treatment for 54 days had a poor response, with marked fluid and electrolyte problems. The diagnosis was mitral insufficiency, slight mitral stenosis, functional tricuspid insufficiency, and marked pulmonary hypertension.

Fifty-four days after admission, a total replacement of the mitral and tricuspid valves was performed in an open-heart operation lasting 12 hr, with total cardiopulmonary bypass on a heart-lung machine.

After this operation, he became hypotensive, required a respirator, developed ischemic changes in the right arm, had a marked deepening of his jaundice, gradually deteriorated, and became anuric. He died 3 days after surgery and 57 days after admission to the hospital.

Necropsy Findings:

1. Aortic valvulitis, chronic, with insufficiency.
2. Cardiac dilatation and hypertrophy, marked, all chambers.
3. Chronic pulmonary disease with pulmonary arteriosclerosis, severe.
4. Dry gangrene, right forearm and hand, probably related to ischemia from brachial artery catheterizations.
5. Acute necrosis with hemorrhage, stomach and bowel.
6. Cardiac cirrhosis.
7. Focal hemorrhagic infarction, liver.
8. Mitral and tricuspid valves not examined; they had been excised at surgery.

SUMMARY OF CASE 660

History: This 64-year-old white man was brought to the hospital by the police shortly after having collapsed on the street. The only history available was that he had had several episodes of coughing, chest and abdominal pain, sweating, and dizziness. The timing of these episodes is unknown.

Physical Examination: He was obese, semicomatose, in acute, severe respiratory distress, and not jaundiced. He was cyanotic and dyspneic with distended neck veins. Pulse was 140. Blood pressure was 70/0. There was abdominal distention, but no mass. All the peripheral arterial pulses were palpable.

Clinical Course: Transferred directly to an intensive-care unit, he remained hypotensive and dependent on Levophed. An electrocardiogram showed no specific pattern, and a dissecting aneurysm of the thoracic aorta was the preoperative diagnosis.

Twelve hours after admission, an emergency left thoracotomy with a De Bakey "reentry" was performed. It consisted of transection and resuturing of the thoracic aorta, done for a completely circumferential dissecting aneurysm of the thoracic aorta, extending from the heart to the diaphragm with hemopericardium.

After surgery he was still hypotensive and comatose, and dependent on Levophed and a respirator. He had a total urine volume of 100 cc in 33 hr. He never regained consciousness, remained hypotensive, gradually deteriorated, was never jaundiced, and died 33 hr after surgery, and 2 days after admission to the hospital.

Necropsy Findings:

1. Aortic arteriosclerosis with dissecting hematoma circumscribing the thoracic aorta, with dissection posteriorly and laterally on the right of the descending aorta to include the right renal artery.
2. Arteriosclerotic fusiform aneurysm of the left common iliac artery.
3. Arteriosclerosis of the coronary vessels with left myocardial hypertrophy, severe, and right myocardial hypertrophy, moderate.
4. Acute toxic nephrosis.
5. Severe pulmonary congestion and edema with atelectasis, diffuse, of lower lobes, bronchopneumonia, and apical emphysema.
6. Serosanguineous pleural effusion: right, 200 cc; left, 200 cc.
7. Fatty change of the liver, mild.

SUMMARY OF CASE 664

History: This 27-year-old white woman entered the hospital for elective cardiac surgery.

At the age of 10, she had had rheumatic fever.

She was in good health until her second pregnancy at 24, when she had a pulmonary embolism. No further details are available about this episode.

Some 15 months before the final admission, tachycardia developed and atrial fibrillation was found. Some 12 months before the final hospital admission, she had open-heart surgery at another hospital, where she allegedly had an "open and shut" operation. Mitral stenosis was diagnosed preoperatively, but she was found to have mitral insufficiency at surgery. No further details are available about that hospitalization.

Some 9 months before the final admission, she had "hepatitis" or "possible homologous serum hepatitis," with "slight jaundice." No other details are available about this episode.

Some 6 months before the final admission she went into acute pulmonary edema and was hospitalized elsewhere.

Since that time, her condition deteriorated with dyspnea, orthopnea, ascites, paroxysmal nocturnal dyspnea, edema, venous congestion, and constant vague abdominal discomfort. One month before the final admission, she had been hospitalized elsewhere for another episode of pulmonary embolism, for which she was treated with anticoagulants until the time of the final admission.

She was taking digitalis, Dicumarol, Diuril, potassium chloride, penicillin, and a mercurial diuretic.

Physical Examination: She was thin, chronically ill, and not jaundiced. Pulse was 88 and absolutely irregular. Blood pressure was 100/75. There were prominent pulsating distended veins in the neck and evidence of cardiac enlargement, with systolic and diastolic murmurs and thrills over the apex and over the lower sternum. The liver was palpable 3 to 4 cm below the right costal margin and was slightly tender.

Clinical Course: She was thought to have rheumatic heart disease with congestive heart failure and mitral insufficiency, tricuspid stenosis, tricuspid insufficiency, aortic stenosis, and cardiac cirrhosis, or chronic hepatitis.

Five days after admission, plastic reconstruction of the tricuspid and mitral valves was performed, with total cardiopulmonary bypass on a heart-lung machine with intentional hypothermia. The valves were repaired by suturing. The operation proceeded with moderate difficulty, and, after surgery, unresponsiveness and insufficient respiration were noticed. A tracheostomy was done under local anesthesia. Supported with a mechanical respirator, she continued to be unresponsive and hypotensive, was treated with hypothermia, gradually deteriorated, was never jaundiced, and died 16 hr after surgery and 6 days after admission to the hospital.

Necropsy Findings:

1. Hemopericardium and hemothorax, bilateral (hemopericardium, 150 cc; right hemothorax, 400 cc; left hemothorax, amount not stated).
2. Fibrinous pericarditis.
3. Rheumatic valvulitis, involving mitral and aortic valves with pseudovalve formation; diffuse pulmonary atelectasis, bilateral (cause of death).
4. Passive congestion of liver, spleen, and kidneys.
5. Anoxic encephalopathy.

SUMMARY OF CASE 665

History: This 53-year-old white man was admitted as a transfer from another hospital with acute onset of abdominal and chest pain, and with a provisional diagnosis of dissecting aneurysm of the thoracic aorta.

With a past history of rheumatic fever at the age of 15, he was found at 21 to have the murmur of aortic stenosis. No congestive heart failure or heart symptoms had been reported.

He was in good health until 1 day before the final admission, when a sudden onset of severe upper abdominal pain, chest pain, and vomiting developed. He was admitted to another hospital, where he was hypotensive. A pericardial tap returned blood, with x-rays showing questionable widening of the mediastinum, and he was thought to have a dissecting aneurysm of the thoracic aorta. Aramine was given for the hypotension, and Demerol, with transferral to the final hospital.

Physical Examination: He was well nourished, sweating, and in pain, but not jaundiced. Pulse was 92 and regular. Blood pressure was 170/? with Aramine running. There was a rough aortic, systolic murmur, and right upper quadrant tenderness, and the liver was tender and palpable 2 cm below the right costal margin.

Clinical Course: An electrocardiogram showed no specific change. He remained hypotensive and dependent on Aramine with increasing right upper quadrant tenderness, rising temperature, and rising WBC, from 15,000 to 40,000. Rheumatic heart disease with aortic stenosis and perforated ulcer, acute cholecystitis, or mesenteric infarction was diagnosed.

Fourteen hours after admission, an exploratory laparotomy was done in which he was found to have thrombosis of the hepatic artery. The procedure included a periarterial sympathectomy of the hepatic artery, cholecystostomy, and liver biopsy, for which no report is available. As the abdominal incision was being closed, he had cardiac arrest, which failed to respond to open-chest cardiac massage with an attempted transventricular aortic valvulotomy. He died in the operating room 2 hr after the start of the operation and 16 hr after admission to the hospital. He was never jaundiced.

Necropsy Findings:

1. Fibrofibrinous pericarditis.
2. Rheumatic carditis with extensive calcific aortic stenosis and marked cardiomegaly, 770 g.
3. Bilateral pulmonary congestion and edema, marked, with pulmonary atelectasis, marked.
4. Passive congestion of the liver and spleen.
5. Toxic nephrosis.
6. Hepatic artery patent.

SUMMARY OF CASE 666

History: This 31-year-old white woman entered the hospital for cardiac surgery.

Since the age of 10, she had been known to have a heart murmur, and from age 17, she had episodes of dyspnea on exertion and paroxysmal nocturnal dyspnea. Her first known episode of rheumatic fever had been at the age of 28. All three pregnancies had been complicated by congestive heart failure and terminated in miscarriages. A tubal ligation was performed, and there were numerous hospitalizations for pneumonia and urinary tract infections.

Some 9 months before the final admission, she was hospitalized elsewhere for 2 weeks with jaundice, nausea, and vomiting, and was thought to have "infectious hepatitis." Further details of this hospitalization are not available. This confinement came less than 6 months after a hospitalization for pneumonia. Attacks similar to this episode of alleged hepatitis did not recur.

She was hospitalized for 1 month, was dismissed, and returned 1 month later for final hospitalization. Right and left cardiac catheterization under local anesthesia were performed, with findings of mitral stenosis and aortic insufficiency. Congestive heart failure with enlargement of the liver to one fingerbreadth below the right costal margin and enlargement of the spleen occurred. Laboratory findings included: hemoglobin, 13.5; PCV, 41; WBC, 7300; prothrombin time, 60 percent; BUN, 11; blood sugar, 98; SGOT, 34; BSP retention, 0 on two occasions; bilirubin, total 0.9 and 3.0 (direct 0.2 and 0.7, indirect 0.7 and 2.3); cephalin flocculation, 3+; thymol turbidity, 10.2; cholesterol, 175; cholesterol esters, 100; C-reactive protein, negative; antistreptolysin 0 titer, 125; sodium, 137; potassium, 5.0; chloride, 107.5; CO_2, 29.5; calcium, 5.5; phosphorus, 3.3; and alkaline phosphatase, 0.6.

On several occasions, a history of "severe alcoholism" was elicited. The only detail available is that she consumed one to two bottles of an unknown alcoholic beverage per week until 3 years before the final admission, when she allegedly stopped using alcohol.

Before the final admission, she had been suffering with increased orthopnea and dyspnea and had been taking digitalis.

Physical Examination: She was thin, chronically ill, and not jaundiced. Blood pressure was 110/60. There were signs of cardiac enlargement, atrial fibrillation, systolic and diastolic heart murmurs, and an opening snap. The liver was palpable two fingerbreadths below the right costal margin and was tender. There was no peripheral edema or venous distention.

Clinical Course: Rheumatic heart disease was diagnosed, with mitral stenosis, aortic insufficiency, atrial fibrillation, and congestive heart failure, compensated. Six days after admission, she underwent surgery for a mitral valvulotomy and then suturing of the mitral valve, with total cardiopulmonary bypass on a heart-lung machine with hypothermia, and a tracheostomy.

From the 1st postoperative day onward she was hypotensive and dependent on Aramine. The left forearm became cool and pulseless, but eventually the pulse returned. From the 2nd day onward, she had high fever and jaundice, and was thought to have possible gram-negative septicemia. Remaining dependent on Aramine, she developed gastric dilatation and passed dark bloody material through the nasogastric tube, but maintained a satisfactory urine volume. The liver became smaller on the 2nd day, but then enlarged on the 3rd day. Signs of pulmonary congestion developed, but no peripheral edema or venous distention. She remained jaundiced and hypotensive, gradually deteriorated, and died 4 days after surgery, and 10 days after admission to the hospital.

Necropsy Findings:

1. Occlusion of the circumflex branch of the left coronary artery due to a suture.
2. Acute myocardial infarction.
3. Pulmonary congestion and edema, severe, with bilateral pleural effusion and moderate ascites.
4. Acute passive congestion of the liver, marked, with marked jaundice.
5. Congestion of the spleen, moderate.
6. Healed rheumatic aortic valvulitis with minimal aortic stenosis.

SUMMARY OF CASE 667

History: This 84-year-old white man entered the hospital because of abdominal pain and distention and vomiting of 1 day's duration.

Five years before the final admission, resection for carcinoma of the sigmoid colon was performed. There was never evidence of recurrence of this tumor.

One and one-half years before the final admission, a small bowel obstruction was diagnosed, and laparotomy with lysis of adhesion was performed under general anesthesia. Postoperatively, he did well until 1 day before the final admission, when abdominal pain and distention and vomiting developed.

Medications taken were digitalis and an unknown medicine for hypertension. He also suffered from Parkinson's disease.

Physical Examination: He was thin and dehydrated, but not jaundiced. Temperature was 97 F, pulse was 60 and irregular, and blood pressure was 150/100. Marked abdominal distention and marked abdominal tenderness, maximum in the left lower quadrant, were evident. The liver was not enlarged or tender.

Clinical Course: X-rays confirmed the impression of small bowel obstruction. One day after admission, exploratory laparotomy was performed with lysis of adhesions, plus a Noble plication of the small intestine (apparently a limited plication). Before and during surgery, the pulse was irregular, and his electrocardiogram showed a number of disturbances of the cardiac rhythm.

After surgery, his temperature spiked to 105 F, with hypotension as low as 0 and abdominal distention with severe pain. He developed rebound tenderness, other evidences of peritonitis, and evidence of pneumonia. He became oliguric and jaundiced, either by the 1st or definitely by the 2nd day. Treated with antibiotics,

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vasopressors, and blood, he gradually deteriorated, and died 3 days after surgery, and 4 days after admission to the hospital.

Necropsy Findings:

1. Infarction of terminal ileum, cecum, ascending and transverse colon, with severe congestion of descending colon.
2. Perforation of the terminal ileum.
3. Serosanguineous fluid in the peritoneal cavity, 200 cc.
4. Severe congestion of the peritoneum.
5. Chronic calculous cholecystitis.
6. Fatty infiltration of the pancreas.
7. Fatty change of the liver.
8. Acute toxic nephrosis.

SUMMARY OF CASE 669

History: This 40-year-old white man entered the hospital as a transfer from another hospital because of weakness, fever, and enlarged lymph nodes of 1 month's duration.

Three months before, he allegedly had "virus pneumonia" and was treated with antibiotics. It is not known whether the antibiotics were by injection or mouth. No further information is available about this illness.

For 1 month, enlarged nontender inguinal lymph nodes were noticed; although no diagnosis had been made, he underwent examinations and numerous blood tests on an out-patient basis.

Some 2 weeks before the final admission, he developed fever to 103 F, abdominal pain and distention, loss of appetite, and a 15-lb weight loss, and was hospitalized elsewhere, found to have ascites, and had paracentesis at least once, producing 4 liters of fluid. A lymph node biopsy showed only "reactive hyperplasia." Laboratory findings at that time included: hemoglobin, 13; RBC, 4.49; WBC, 8100; BSP retention, 30.5 percent; BUN, 20; blood sugar, 104; sodium, 124; potassium, 6; bilirubin, 0.8; total protein, 5.4; albumin, 3.9; globulin, 1.5; alkaline phosphatase, 2.5; SGOT, 23; and Paul-Bunnell test, negative.

Physical Examination: He was acutely ill, pale, weak, and "sallow," but not definitely jaundiced. Blood pressure was 100/60 and pulse was 120. He had enlarged lymph nodes in the neck, axillas, and groins. There was abdominal distention with questionable ascites. The liver and spleen were not palpable.

Clinical Course: He was thought to have probably a lymphoma, generalized infection, or both. Within a few hours of admission, he suddenly had massive lower gastrointestinal bleeding. He had a fall in PCV from 27 to 20 and a fall in blood pressure from 110 to 85, and had a transfusion, but continued to bleed. A nasogastric tube was passed and produced dark blood. The decision to operate was made while he was deteriorating.

One day after admission he underwent exploratory laparotomy with gastrotomy and gastrostomy, pyloroplasty, and vagotomy. No specific bleeding point was found. He was found to have enlarged lymph nodes throughout the abdomen and the omentum, and the lymph nodes were biopsied, showing malignant lymphoma.

After this, he continued to bleed by rectum, never had purpura or bleeding from the incision, and was treated with a Blakemore-Sengstaken tube and irrigation of his stomach with iced saline. He was never jaundiced. His urine output ceased. He had cardiac arrest and died 1 day after surgery, and 2 days after admission to the hospital.

Necropsy Findings:

1. Lymphosarcoma, lymphoblastic type, with involvement of mediastinum, retroperitoneal, peritoneal, para-aortic, cervical, axillary, and inguinal lymph nodes, liver, and spleen.
2. Ulcers, acute, multiple, stomach with massive gastrointestinal hemorrhage.
3. Atelectasis, marked, of lower lobes of both lungs.
4. Necrosis, focal, multiple, liver.

SUMMARY OF CASE 670

History: This 50-year-old white man was admitted to the hospital because of cough and shortness of breath.

He had been known to have hypertension for 4 years.

Three years before, he underwent surgery for left nephrectomy, because of a nonfunctioning left kidney, and left lumbar sympathectomy.

For 4 months, he was known to have a blood pressure of 190/100, cardiac enlargement, absence of the right femoral pulse, and a bruit over the aorta, and had been taking digitalis, chlorothiazide, Peritrate, and Ismelin.

Because of a 1-month history of cough and shortness of breath, increasing in severity for 1 week, he entered the hospital. X-ray had shown a right pleural effusion, and he was treated with tetracycline and aminophylline.

Physical Examination: He was thin, dyspneic, orthopneic, and coughing, but not jaundiced. Blood pressure was 180/120. There were signs of bilateral pulmonary congestion, a right pleural effusion, and emphysema. There was right upper quadrant tenderness and slight clubbing and cyanosis of the extremities, but the liver was not definitely palpable. The right femoral pulse was absent and the left femoral pulse was weak. There was a bruit over the aorta and the left femoral artery.

Clinical Course: The day after admission, an episode of chest pain, nausea, and vomiting ensued, and an electrocardiogram showed an acute myocardial infarction that was later confirmed by the elevations in the SGOT and LDH. This was medically treated, including anticoagulants. Three weeks later, a second episode of epigastric distress and nausea occurred, with another increase in SGOT and LDH, and he was thought to have a second myocardial infarction. Blood in his stools continued, and on about the 30th day, he was given 1500 cc of blood. Enlargement of the liver, pulmonary congestion, and edema followed. On the 33rd day, 3 days after the anticoagulants were stopped, severe pain in his legs, absent femoral pulses, and cold feet developed.

An emergency exploratory laparotomy was performed, with thromboendarterectomy and embolectomy of the aortic bifurcation and the proximal portions of the arteries, and thrombosis of these vessels was found. He died as the incision was being closed, 90 min after the induction of anesthesia, and 33 days after admission to the hospital. He was never jaundiced.

Necropsy Findings:

1. Arteriosclerosis, severe, of the coronary arteries, with old healing and recent myocardial infarctions.
2. Arteriosclerosis, severe, of the aorta, with fusiform aneurysm of the abdominal aorta, and underlying mural thrombus.
3. Arteriosclerosis, severe, of iliac arteries, with thrombotic occlusion of right common and internal iliac arteries.
4. Arteriosclerosis, severe, of renal arteries, with marked narrowing of the ostium of the right renal artery.
5. Nephrosclerosis, arterial and arteriolar, advanced.
6. Emphysema, severe, pulmonary.
7. Pulmonary congestion, chronic, passive, slight.
8. "There was a beautiful nutmeg change in the liver." (No other description of the liver available.)

SUMMARY OF CASE 673

History: This 68-year-old white woman entered the hospital for the eighth time because of weight loss, loss of appetite, and abdominal pain.

Five years before the final admission, a right radical axillary lymph node dissection was done for adenocarcinoma originating in the axillary sweat glands. She had been followed in a tumor clinic with no sign of recurrence. The liver was not enlarged at that time.

She had a history of arteriosclerotic cardiovascular disease with congestive heart failure for many years, and had been on digitalis and diuretics with symptoms including dyspnea on exertion and orthopnea, but paroxysmal nocturnal dyspnea or edema was not included.

A corneal transplant was done. Liver function tests were described as "normal" at that time.

Her entrance into the hospital was necessitated because of a 4-month history of a 37-lb weight loss with anorexia and vomiting for 3 weeks, and epigastric pain for 2 or 3 days.

Physical Examination: She was obese and not jaundiced. Blood pressure was 90/60. There were signs of pulmonary congestion. The liver was enlarged to five fingerbreadths below the right costal margin and was slightly tender, with a "golf ball sized" nodule palpable in the left lobe. There was evidence of a previous right axillary lymph node dissection without evidence of recurrence, and edema of both lower extremities.

Clinical Course: Preoperative diagnoses were thought to be congestive heart failure and metastases to the liver, although it was not clear whether these came from the lesions seen in the cecum on x-ray or from the previous carcinoma in the axilla.

Seven days after admission, a needle liver biopsy was done, which showed "fatty change, portal fibrosis, and focal necrosis." This was unsatisfactory, so on the 11th day she had a second needle liver biopsy, which showed "liver with fatty change and metastatic adenocarcinoma."

Twenty-one days after admission, a right colectomy procedure was done in which she was found to have a large carcinoma of the cecum with involvement of the mesentery and numerous lymph nodes and the liver, by numerous metastases.

After this, she did reasonably well, except for low-grade fever, poor cough, and poor cooperation. On the 14th day she suddenly became hypotensive and died. She was never jaundiced. She died 14 days after surgery, and 45 days after admission to the hospital.

Necropsy Findings:

1. Focal pneumonitis.
2. Metastases to the liver.
3. Thrombosis of the inferior vena cava and portal veins.
4. Abscess in peritoneal cavity beneath the surgical incision.

SUMMARY OF CASE 675

History: This 80-year-old woman entered the hospital directly following a fall in which she sustained a fracture of the left hip.

She was known to have arteriosclerosis, with cardiac enlargement, left bundle branch block, emphysema, and diabetes, controlled by diet without insulin. She had been having an increasing number of falls recently.

Physical Examination: The patient was obese, alert, and not jaundiced. Blood pressure was 220/130. There was no abdominal mass or tenderness but pain occurred with motion of the left hip.

Clinical Course: On the day after her admission she became dehydrated and confused. Three days after admission she underwent open reduction and internal fixation of the extremely comminuted intertrochanteric fracture of the left hip with a Massey nail. After this, she did well until the 17th day, when the x-rays showed that the nail had slipped out of the head of the femur and into the acetabulum. A number of transfusions in preparation for a second operation were given, because she was found to be anemic.

Twenty-six days after the first operation, a second operation was performed, consisting of removal of the nail with insertion of a Steinmann pin in the left tibia, and she was placed in traction. Nine days later, a wound infection was found and she continued with fever and increasing purulent drainage, and developed a urinary tract infection and bed sores.

Twenty-one days after the second operation, she had a third operation under general anesthesia, in which she was placed in "well-leg traction," as an alternative to the usual type of traction. She continued with dehydration and fever, had a positive blood culture, developed marked generalized edema, oliguria, marked fluid and electrolyte problems, pulmonary congestion, and increasing bed sores, gradually deteriorated, was not hypotensive, and was never jaundiced. She died 21 days after operation 3, 48 days after operation 2, 74 days after operation 1, and 77 days after admission to the hospital.

Necropsy Findings:

1. Transverse fracture of the surgical neck of the left femur.
2. Osteomyelitis of the left femur with abscess.
3. Thrombosis of the left femoral vein.
4. Septicemia.
5. Multiple decubiti.
6. Myocardial infarction.
7. Recent, acute infarct of cerebral cortex.
8. Hemorrhagic dissection of the arch of the aorta.
9. Pulmonary congestion and edema.
10. Multiple, organizing pulmonary emboli.
11. Chronic passive congestion of the liver.

SUMMARY OF CASE 680

History: This 50-year-old woman entered the hospital with a history of swelling of both sides of the neck for 3 weeks.

She had a long history of smoking and chronic cough, and for 3 months had had an increasing amount of coughing with fever. Diagnosis of bronchitis was made and treatment with antibiotics produced no improvement. It is not known whether the antibiotics were given by mouth or injection.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 140/80. There were bilateral cervical and right supraclavicular lymph nodes that were enlarged and palpable, with no abdominal mass or tenderness.

Clinical Course: X-rays showed a probable carcinoma of the left lung. Bronchoscopy under local anesthesia showed widening of the carina and extrinsic compression of the left main stem bronchus.

Four days after admission, a biopsy of the right cervical lymph nodes under general anesthesia showed carcinoma metastatic to the lymph nodes and muscles of the neck.

Radiation therapy followed. From the 11th day onward, she was weak, aphasic, confused, and paralyzed on the right side. She gradually deteriorated, had increasing respiratory distress, was never hypotensive and never jaundiced, and died 17 days after surgery, and 21 days after admission to the hospital.

Necropsy Findings:

1. Thromboembolism with thrombi in hepatic, splenic, and left middle cerebral arteries.
2. Carcinoma of the lung, with widespread metastases to lung, hilar, peritracheal, esophageal, cervical, aortic, and mesenteric lymph nodes, subcutaneous tissues of the neck, adrenals, spleen, and liver.
3. Ischemic infarct of the brain.
4. Infarct of the kidneys.
5. Tumor in the pericardium with fibrinous pericarditis and pericardial effusion.
6. Pulmonary edema and bilateral pleural effusion.
7. Central lobular necrosis and passive hyperemia of the liver.

SUMMARY OF CASE 681

History: This 53-year-old white man entered the hospital for evaluation for possible cardiac surgery.

For 18 months, he had been having typical angina pectoris.

One year before admission, he underwent bilateral ligation of the internal mammary arteries and showed no improvement.

Severity in the symptoms increased, necessitating his taking 50 nitroglycerin tablets per day.

No history of congestive heart failure or jaundice was given.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 180/105. There were signs of cardiac enlargement. There were no abdominal masses or tenderness.

Clinical Course: A left stellate ganglion block was performed, with marked relief of his angina. An electrocardiogram showed the chronic changes of coronary artery disease and also of a questionable recent evolving myocardial infarction, but possibly this was not appreciated at the time.

Five days after admission, a left dorsal sympathectomy with pericardial poudrage was done. At this operation, a hemorrhagic area in the left ventricle was found and considered to be evidence of a recent myocardial infarction.

After surgery, the electrocardiogram showed further evidence of the myocardial infarction. Remaining hypotensive and cyanotic, he required increasing doses of vasopressors, became confused, had continuing chest pain, was never jaundiced, and died 2 days after surgery, and 7 days after admission to the hospital.

Necropsy Findings:

1. Arteriosclerotic cardiovascular disease with recent coronary occlusion due to hemorrhage in the atherosclerotic plaque with myocardial infarction.
2. Pericarditis.
3. Hyperemia of the liver with central lobular necrosis.

SUMMARY OF CASE 685

History: This 70-year-old white man entered the hospital because of an upper abdominal mass that had been present for 3 or 4 months.

A gradually increasing mass in the upper abdomen for 3 or 4 months was apparent, but no pain was felt. There had been a 25-lb weight loss and, because of general weakness, he was bedridden for 6 weeks before the final hospital admission. There had been no hospitalization or specific treatment before admission, and no jaundice had been noted.

Physical Examination: He was emaciated, dehydrated, and chronically ill, but not jaundiced. Blood pressure was 170/100. There was a hard, midline, epigastric mass. The liver was not palpable.

Clinical Course: X-rays showed a probable carcinoma of the stomach with complete gastric outlet obstruction. He was found to be anemic and was treated with intravenous fluids, nasogastric suction, and blood. He accidentally received 20 to 25 cc of blood intended for a different patient, without detectable reaction.

Six days after admission, he underwent exploratory laparotomy and palliative gastrojejunostomy, with a feeding jejunostomy and a gastrostomy for suction. A large carcinoma of the stomach involving the greater omentum and transverse mesocolon was found.

He was hypotensive on the 1st day, then normotensive for several days. He developed evidence of left lower lobe pneumonia, was treated with antibiotics, and was fed through his jejunostomy, but on the 5th day developed evidence of increasing respiratory distress and became comatose and hypotensive. He remained hypotensive the last 2 days of life, gradually deteriorating, was never jaundiced, and died 7 days after surgery, and 13 days after admission to the hospital.

Necropsy Findings:

1. Carcinoma of the stomach, poorly differentiated, invading gastrocolic and gastrohepatic ligaments, with lymph node metastases.
2. Bronchopneumonia and pulmonary hemorrhage, focal pulmonary collapse, and patch necrosis, left lower lobe.
3. Pulmonary emphysema, moderately severe.
4. Tracheobronchitis, moderately severe, with partial bronchial mucous obstruction.
5. Generalized peritonitis.
6. Coronary arteriosclerosis, severe.
7. Cirrhosis of the liver, Laennec type, early, mild, and patchy necrosis (microscopic diagnosis).

SUMMARY OF CASE 686

History: This 71-year-old man entered the hospital shortly after falling 10 ft through a hole in the floor into a basement, landing on a saw horse, and suffering immediate pain in the back and inability to move his legs.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 120/70. There was a gibbous deformity in the upper lumbar spine, and no abdominal mass or tenderness. There were decreased breath sounds over the left side of the chest. The right lower extremity was paralyzed, but the left was not. He had decreased sensation over the right lower extremity and over the left foot.

Clinical Course: X-rays showed fractures of multiple ribs and of the 12th thoracic and first lumbar vertebral bodies. Conservative treatments were given and he was observed for possible other injuries. He did well until the 4th day, when he suddenly became hypotensive, with rapid pulse and respiration, and was thought by physical findings and x-ray to have a left hemothorax.

On the 4th day, he underwent emergency left thoracotomy, with evacuation of 2000 cc hemothorax, which was coming from the fractured vertebral bodies. The diaphragm was found to be intact, but the upper abdomen was explored through the diaphragm, and a ruptured spleen removed. During this operation, his estimated blood loss was 4000 cc, and blood replacement was 6000 cc. The possibility of over-transfusion was discussed.

Postoperatively, his condition was poor. He was plethoric and showed cyanosis of the upper half of his body and hypotensiveness. He showed an elevated venous pressure, and had multiple tourniquets applied and phlebotomy, but deteriorated and died 7 hr after surgery, and 5 days after admission to the hospital. He was never jaundiced.

Necropsy Findings:

1. Extensive pulmonary collapse, severe pulmonary congestion, and intra-alveolar hemorrhage, moderately severe pulmonary edema, mild pulmonary emphysema.
2. Fracture of vertebral spine T_{12}, L_1, and compression injury to spinal cord.
3. Central lobular necrosis and hepatic congestion and edema.
4. Left ventricular myocardial hypertrophy.

Comments by Pathologist: "In the presence of rather severe left ventricular hypertrophy, it appears that the mechanism which led to death was an acute left ventricular cardiac failure with the increased blood volume and the consequent congestion and hemorrhage in the pulmonary circulation. As to what extent possible over-transfusion has contributed to this event cannot be stated, but it is likely to be of some significance in view of the increased hemoglobin and hematocrit values obtained shortly before death."

SUMMARY OF CASE 687

History: This 48-year-old white man entered the hospital as a transfer from another hospital with the problem of duodenal ulcer.

For 20 years he had had duodenal ulcer symptoms, and he had been hospitalized 15 and 13 years before the final hospitalization for duodenal ulcer.

Six months before the final hospital admission, he had been hospitalized elsewhere for duodenal ulcer, and was treated medically.

His ulcer symptoms had been very severe for 2 weeks before the final hospital admission; he had vomited blood once and had lost 20 lb. He had been hospitalized elsewhere 10 days before the final admission. Laboratory findings then were: hemoglobin, 13.0; RBC, 4.17 million; WBC, 9500; amylase, 70; and icteric index, 4.3.

He was treated with Pro-banthine, Oxaine, Donnatal, Riopan, morphine, and Thorazine.

No history of jaundice or gastrointestinal bleeding was given.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 140/100. There was no abdominal mass or tenderness.

Clinical Course: X-rays showed pyloric obstruction. He was treated medically, with nothing by mouth, nasogastric suction, and intravenous fluids, without improvement.

Six days after admission, he had operation 1, which was a 60 percent subtotal gastric resection, with a gastrojejunostomy, a feeding jejunostomy, and a drainage jejunostomy.

After this, his temperature spiked to 103 F, with cough and signs of pulmonary congestion. He responded to antibiotics and endotracheal suction. On the 4th day he developed first right chest pain and then generalized abdominal pain with abdominal tenderness and rebound tenderness. On the 5th day, the left leg was numb, cold, and mottled, and the left femoral and other pulses on the left leg had disappeared.

Accordingly, he was returned to surgery 5 days after operation 1 for operation 2, a thrombectomy of the left common iliac artery, with an exploratory laparotomy, in which he was found to have generalized purulent peritonitis. The bowel was described as hemorrhagic but not necrotic. He also had drainage of bilateral subphrenic abscesses at this time.

After operation 2, he was treated with heparin and antibiotics. He became oliguric and on the 1st day became jaundiced for the first time and confused. He became hypotensive and more deeply jaundiced, gradually deteriorated, and died 3 days after operation 2, 8 days after operation 1, and 14 days after admission to the hospital.

Necropsy Findings:

1. Generalized purulent peritonitis.
2. Congestion and necrosis, small and large intestine (infarction of the intestine).
3. Atherosclerosis with ulceration and thrombosis of the abdominal aorta to 4 cm above the celiac artery.
4. Central lobular necrosis of the liver.
5. Focal pneumonia and collapse of lungs.
6. Early tubular necrosis, kidneys.

SUMMARY OF CASE 688

History: This 77-year-old white woman entered the hospital because of constipation, weakness, weight loss, and the finding of an abdominal mass.

Four years before she had been admitted to the same hospital for a radical mastectomy for carcinoma of the right breast. At that time she was found to have a calcified pelvic mass, about which nothing specific was done.

She entered finally with a 1-year history of constipation, with increasing need for laxatives and decreasing caliber of her stools. She had a 1-month history of right lower quadrant pain, worse with standing, a poor appetite, and a 20-lb weight loss. A barium enema showed a constricting lesion in the sigmoid colon.

Physical Examination: She was well nourished and not jaundiced. Blood pressure was 130/60. The abdomen showed moderate right upper quadrant tenderness on a single examination only, but no mass. Pelvic examination showed a rock-hard, fixed, tender mass on the left side of the pelvis. There was no sign of recurrent carcinoma of the breast.

Clinical Course: She was studied in the hospital for 12 days before surgery, and found to have the calcified pelvic mass, as shown before, and a constricting lesion in the sigmoid colon with an enterocolic fistula. Preoperative diagnosis was thought to be a calcified uterine fibroid or dermoid with pelvic inflammatory disease and/or diverticulitis with complications.

Twelve days after admission, an exploratory laparotomy was performed. She was found to have an inflammatory mass involving the sigmoid colon and bladder, thought to be the basis of diverticulitis, and a cystic mass of the right ovary, thought to be carcinoma but later shown to be inflammatory. A 12-in. segment of small bowel involving two areas of obstruction and a fistula was resected. A transverse colostomy and a suprapubic cystostomy were done for an accidental perforation of the bladder. It was noted at surgery that there was poor blood supply to the small intestine.

After surgery, she was hypotensive, cyanotic, and oliguric, gradually deteriorated, was never jaundiced, and died 2 days after surgery and 14 days after admission to the hospital.

Necropsy Findings:

1. Infarction, large and small bowel, extensive, early.
2. Hemoperitoneum, 400 cc.
3. Collapse, pulmonary, right and left lower lobes.
4. Dermoid cyst, right ovary, so situated as to cause constricting angulation of the sigmoid colon (size not stated).
5. Bronchopneumonia, left.
6. Central lobular necrosis, liver.
7. Acute tubular necrosis, early.
8. "No evidence of thrombosis seen in mesenteric vessels." No comment, otherwise, as to the condition of the abdominal vessels.

SUMMARY OF CASE 689

History: This 68-year-old white man was readmitted for elective thoracic surgery for bronchiectasis.

He had a 1-year history of spells of dizziness, nausea, and vomiting, and had been found unconscious 2 months before the final hospital admission.

One month before the final admission, he had been admitted for evaluation for 7 days. During this time, he was found to have a chronic cough, producing 2 to 3 oz of purulent sputum per day. Bronchoscopy showed blood in the left main stem bronchus, and bronchograms showed nonfilling of a superior segmental bronchus of the left lower lobe. A gallbladder series was negative and a number of other studies were done pertaining to the dizziness but no specific diagnosis was made. Surgery for the presumed bronchiectasis was advised.

Physical Examination: He was confused and obese, but not jaundiced. Blood pressure was 140/40. There were decreased breath sounds and rales over the left lower lobe. The liver was palpable two fingerbreadths below the right costal margin, but was not tender.

Clinical Course: One day after admission a left lower lobectomy was done for what proved to be bronchiectasis.

Postoperatively, he did well until the 5th day, when a rash and bronchospasm developed, which were thought to be a reaction to penicillin. He was treated medically for this, but later developed dyspnea, increasing difficulty in clearing respiratory tract secretions, increasing cough, temperature to 103 F, cyanosis, blood-streaked sputum, and, finally, pulmonary edema. He did not have enlargement of the liver or peripheral edema. Vigorous medical treatment followed. He was never jaundiced and was hypotensive only on the last day of life. He died 8 days after surgery, and 9 days after admission to the hospital.

Necropsy Findings:

1. Bronchopneumonia, necrotizing, hemolytic Staphylococcus aureus.
2. Empyema, hemolytic Staphylococcus aureus.
3. Postthoracotomy wound infection with hemolytic Staphylococcus aureus.
4. Septicemia.
5. Septic splenitis.
6. Central lobular necrosis and acute inflammation of the liver.
7. Visceral congestion.
8. Cystic degeneration, old, focal, left frontal lobe of brain.

SUMMARY OF CASE 691

History: This 64-year-old white man entered the hospital because of difficulty and hesitancy in urinating for 4 months.

For 2 years before, he had been known to have an aneurysm of the abdominal aorta. No treatment had been given and no change was shown.

TACE, a synthetic estrogen, was the medication used for 1 year, for reasons unknown.

Physical Examination: He was well nourished and not jaundiced, with signs of emphysema and gynecomastia. The liver was not palpable. Blood pressure was 140/80. There was a pulsating aneurysm of the abdominal aorta. The bladder was palpable to the umbilicus. The prostate was enlarged and very hard.

Clinical Course: X-rays showed possible metastases to the spine. He was catheterized and found to have a residual urine volume of 850 cc.

Seven days after admission, a bilateral orchiectomy under caudal plus general anesthesia was performed. Postoperatively, he had nausea and pain in his low back, hip, and knee. In addition, he had some vomiting and abdominal pain.

Five days after the first procedure, he had a second operation, a transurethral resection of the prostate under general anesthesia. He continued to have pain in the back and left leg postoperatively. On the 5th day, he complained of

dizziness and vomiting, and passed gross blood in the urine. On the 6th day, he became dyspneic and hypotensive, had increasing back pain, and remained hypotensive. He died 6 days after operation 2, 11 days after operation 1, and 18 days after admission to the hospital. He was never jaundiced.

Necropsy Findings:

1. Carcinoma of the prostate with metastases to the vertebral column, T_{8-9}, and lungs.
2. Emphysema, chronic, bilateral, with thickening of pulmonary arterial and arteriolar walls, calcification in arterial walls, and occlusion of some arterioles, and with minimal thickening of the right ventricular wall.
3. Chronic passive congestion of the liver, with central lobular necrosis, acute.
4. Generalized atherosclerosis, moderate, with narrowing of the coronary arteries, diffuse interstitial myocardial fibrosis, and mild calcific changes of aortic and mitral valves.
5. Saccular abdominal aneurysm, originating below the renal arteries, with mild extravasation retroperitoneally, with no free blood in the peritoneal cavity and no rupture.
6. Superficial ulceration of the stomach with gastrointestinal hemorrhage, 800 cc.
7. No sign of myocardial infarction.

Comments by Pathologist: "Blood loss was insufficient to explain the shock, and we are left with only speculation as to its etiology. These include a gram-negative sepsis or a cerebral disorder, since no examination of the brain was permitted."

SUMMARY OF CASE 692

History: This 63-year-old white man was admitted to the hospital because of vomiting of blood for 5 hr.

He had suffered from a myocardial infarction 10 years before the final admission, and since then had had angina and was taking nitroglycerin and Peritrate.

On admission 21 months before, he had undergone excision of an aneurysm of the abdominal aorta, extending from below the renal arteries to the iliac arteries, and replacement with a Dacron Y-graft. This operation involved transfusion of 4500 cc of blood. There was no mention of enlargement of the liver in this hospitalization, and the operative report did not mention the liver. At this time, hemoglobin was 11.0; RBC, 3.95 million; WBC, 8000; blood sugar, 105; and BUN, 35. There were no liver function tests.

Because of left chest pain, he had been admitted to another hospital approximately 1 year before the final admission. Thoracentesis produced 5 quarts of whitish fluid and the diagnosis of chylothorax was made. The underlying cause of this was never determined and the condition cleared with a tube thoracostomy.

Seventeen years before the final admission, he had been known to have a duodenal ulcer manifested by abdominal pain. This was treated medically with relief, and ulcer symptoms did not return.

Having vomited bright red blood, he was admitted, finally, to the hospital. Five hours later, he developed sharp stabbing pain in the upper abdomen, radiating to the back.

Physical Examination: He was obese and not jaundiced. Blood pressure was 140/80. The abdomen showed midline epigastric tenderness. The liver was not palpable.

Clinical Course: He was treated conservatively medically and appeared to be stable initially. On the 2nd day, he again vomited blood, became hypotensive to 80/50, and showed a fall in PCV from 34 to 26. He was thought to have duodenal ulcer, or recurrent aneurysm of the abdominal aorta, or weakening of the suture line of the previous graft with erosion into the duodenum.

Two days after admission, an emergency exploratory laparotomy was performed in which he was found to have a 10 x 12-cm bulging recurrent aneurysm of the abdominal aorta, with the transverse portion of the duodenum wrapped around it, containing a bleeding ulcer. The aneurysm was resected and replaced by a graft. All of the duodenum except the upper half of the first portion was resected, and a duodenojejunostomy done. The aorta was clamped above the renal artery for an unknown period, but the resection and graft were from below the renal artery to the distal portion of the previous graft. During this operation, he received a large amount of blood and a Neo-synephrine drip to support blood pressure.

Immediately after surgery, his pressure was in the normal range, but from the 1st day onward, he was hypotensive and dependent on vasopressors. He was also oliguric and was treated with fluid restriction. He continued this way until the 3rd day, when he had cardiac arrest. He was resuscitated with closed-chest cardiac massage, had a tracheostomy, remained unresponsive, anuric, and dependent on a respirator, and became increasingly hypotensive. He died 3 days after surgery, and 5 days after admission to the hospital. He never was jaundiced.

Necropsy Findings:

1. Atherosclerosis, generalized, severe.
2. Acute tubular necrosis of the kidneys.
3. Acute, extensive centrilobular hepatic necrosis.
4. Hemoperitoneum, 1500 cc.
5. Hemorrhage into adrenal medulla, bilateral.

6. Infarction of the descending colon.
7. Thrombosis of the splenic vein.
8. Pulmonary edema and congestion, moderate.
9. Acute peptic ulceration of the fundus of the stomach.

SUMMARY OF CASE 707

History: This 21-year-old white man was admitted for elective cardiac surgery.

He had always been known to have a heart murmur, and had always suffered from dyspnea on exertion, fatigue on exertion, and mild cyanosis with exertion. These symptoms had been gradually increasing in severity.

Six months before the final hospitalization, he was admitted for cardiac catheterization, which yielded the diagnosis of interventricular septal defect with infundibular pulmonary stenosis.

Physical Examination: He was well nourished, not jaundiced, and not cyanotic. Blood pressure was 120/80. There was systolic murmur and thrill.

Clinical Course: Seven days after admission, he underwent an infundibular resection and repair of an interventricular septal defect, with total cardiopulmonary bypass on a heart-lung machine and hypothermia. This operation was unusual, in that it lasted 10 hr and there was more difficulty with bleeding than usual.

After this operation, bleeding continued and x-ray showed evidence of widening of the mediastinum.

Thirty-six hours after the first operation, a second operation was performed: reopening of the thoracotomy with attempted control of multiple bleeding points in the thymus, pleura, and sternum.

Following this procedure, he was oliguric, as he had been before the second operation, remained hypotensive, and continued to bleed through the chest tubes and from the incision. Dialysis on an artificial kidney was considered but not done because of his bleeding tendency. Bleeding continued, he remained dependent on vasopressors, and he had cardiac arrest, which failed to respond to external cardiac massage. Never jaundiced, he died 2 days after operation 2, 3 days after operation 1, and 10 days after admission to the hospital.

Necropsy Findings:

1. Tetralogy of Fallot, postoperative.
2. Shock kidney (renal tubular hydropic change).
3. Pneumonia.
4. Mediastinal hemorrhage.
5. Pleural hemorrhage.
6. Passive congestion of the liver.

SUMMARY OF CASE 709

History: This 37-year-old white woman entered the hospital for evaluation for possible cardiac surgery.

She had been well until 21 months before the final hospital admission, when she developed chest pain and a left pleural effusion.

Fourteen months before the final admission, she had two episodes of paroxysmal nocturnal dyspnea, dyspnea on exertion, and fatigue on exertion, was started on digitalis and Diuril, and, following this, did well.

Nine months before the final admission, she began to have numerous respiratory infections.

Before the final hospitalization, she was admitted elsewhere for a 1-month stay, with pneumonia. At that time, she had her first cardiac catheterization, which showed pulmonary hypertension, no evidence of a shunt, and suggestion of a patent ductus arteriosus.

She had been at home for 1 month before the final admission, during which time she had another episode of pneumonia, with fever and dyspnea.

Her final admission was due to dyspnea, edema, fatigue, and a 25-lb weight loss in 14 months. She had no history of rheumatic fever and had never been known to have a heart murmur before.

Digitalis, Hydrodiuril, potassium chloride, Cafergot for migraine, aspirin, Darvon, codeine, and Compazine were the medications she had been taking. Compazine in unknown dosages was taken for an unknown period.

Physical Examination: She was thin and not jaundiced with a regular pulse of 72, temperature of 99 F, and blood pressure of 100/70. There were systolic and diastolic murmurs. The liver was palpable 8 cm below the right costal margin and was not tender.

Clinical Course: On the day of admission, she developed fever to 102.8 F and had thoracentesis of 420 cc of clear fluid, which was negative on culture and on examination for malignant cells. Under local anesthesia she had a tube thoracostomy, which remained in place for 3 days.

Four days after admission, a second cardiac catheterization, which was a left-heart catheterization, was performed under local anesthesia and showed acute rupture of the chordae tendinae, for which she was treated conservatively. She was also thought to have possible pulmonary emboli, for which she was treated with anticoagulants.

Thirty-six days after admission, operation 1, a third catheterization, being a right-heart catheterization, was performed under general anesthesia, and showed pulmonary hypertension and signs of mitral stenosis and insufficiency.

One day following the first procedure, she had operation 2, excision of the mitral valve and

replacement with a ball-valve prosthesis, performed with total cardiopulmonary bypass on a heart-lung machine with hypothermia to 29 C. During this procedure, cannulation of the femoral artery was attempted twice with difficulty and finally abandoned. The subelavian artery was eventually cannulated and eventually ligated.

One day later, she bled from the femoral artery, necessitating operation 3, exploration of the groin with evacuation of a 1000-cc hematoma and ligation of a small arterial branch of the femoral artery.

After operation 3, she continued with moderate hypotension, severe pain in the right lower quadrant, and tachycardia. She continued to bleed from the right groin, which was opened under no anesthesia and evacuated of a hematoma. A cardiac arrest followed, which responded to external cardiac massage. Terminally, she had gastrointestinal bleeding, gradually deteriorated, and was never jaundiced. She died 1 day after operation 3, 2 days after operation 2, 3 days after operation 1, and 39 days after admission to the hospital.

Necropsy Findings:

1. Mitral valve excised and replaced with a total prosthesis.
2. Retroperitoneal hematoma.
3. Hemoperitoneum.
4. Ischemic necrosis of the liver.
5. Severe chronic passive congestion of the lungs.
6. Old, small pulmonary infarcts.
7. Hemorrhagic gastroenteritis.
8. Subarachnoid hemorrhage.
9. Hydropic degeneration of the proximal tubules of the kidneys.
10. Inactive rheumatic heart disease with previous mitral insufficiency.

SUMMARY OF CASE 711

History: This 33-year-old man entered the hospital as a transfer from another hospital 3 days after the closure of a perforated duodenal ulcer.

Ulcer symptoms had been noticeable for 9 years.

Three days before transfer to the final hospital, he entered the first hospital with perforated duodenal ulcer, for which he underwent surgery quite promptly, under an unknown type of anesthesia, and consisting of closure of the ulcer. After surgery, he became oliguric, with urine volumes of 250, 250, and 100 cc per 24 hr. He was treated with fluids and electrolyte solutions, but not plasma or blood, became dehydrated, and showed signs of generalized peritonitis with distention, ileus, and pain.

Physical Examination: He was obese and not jaundiced. Blood pressure on arrival was 0. The extremities were cold and mottled. The abdomen was distended and silent, with a fluid wave. The liver was not palpable.

Clinical Course: He was treated with 1500 cc of plasma in 2 hr with restoration of his blood pressure. Paracentesis produced 3 liters of brown fluid with an amylase of 146. X-rays showed free air, free fluid, and a suggestion of an abscess in the right upper quadrant.

The day after transfer to the final hospital, and 4 days after the first operation, a second operation was performed for reclosure of the perforated duodenal ulcer, with a pyloroplasty and cholecystectomy. He was found to have an open ulcer in the duodenum, with a perforated gallbladder, which apparently had been adherent to the perforation in the duodenum.

After operation 2, he did reasonably well until the 8th day, when gastrointestinal bleeding started, which was treated conservatively without improvement. Therefore, 8 days after operation 2, operation 3 was performed: a transthoracic, bilateral, truncal vagotomy.

Postoperatively, he had massive lower gastrointestinal bleeding and became hypotensive. Two days after operation 3, he underwent operation 4, a 50 percent subtotal gastrectomy and a splenectomy, done for several bleeding gastric ulcers. He was hypotensive, maintained a good urine volume, required vasopressors, was never jaundiced, had cardiac arrest, and died 1 day after operation 4, 3 days after operation 3, 11 days after operation 2, 12 days after transfer to the final hospital, and 15 days after operation 1.

Necropsy Findings:

1. Staphylococcal bacteremia.
2. Massive pulmonary atelectasis and bronchopneumonia.
3. Acute purulent tracheitis.
4. Scattered areas of hepatic infarction.
5. Small areas of peripancreatic fat necrosis.
6. Peritonitis.
7. Esophageal erosion.

SUMMARY OF CASE 712

History: This 19-year-old white girl entered the hospital for elective cardiac surgery.

She had been known to have heart disease since infancy, which was manifested by cyanosis and dyspnea on exertion.

Eighteen months before the final hospitalization, she had been admitted for cardiac catheterization. At that time, she had cyanosis and a systolic murmur, but no enlargement of the liver. Cardiac catheterization and angiocardiography showed valvular and infundibular pulmonic stenosis with no septal defect. It was thought that the cyanosis was due to a small atrial septal defect or a patent foramen ovale with two-way flow due to the high pressure on the right side of the heart.

On her final admission for elective cardiac surgery, she had had no progression of symptoms, nor any history of congestive heart failure.

Medications included monthly prophylactic injections of penicillin.

Physical Examination: She was well nourished (weight, 112 lb), cyanotic, and not jaundiced. Blood pressure was 100/60. There was a systolic murmur. There was no abdominal mass or tenderness.

Clinical Course: Eight days after admission, she underwent closure of an interatrial septal defect, infundibular resection, and pulmonary valvulotomy, with plastic reconstruction of the right ventricular outflow tract, with a patch, performed with total cardiopulmonary bypass on a heart-lung machine with hypothermia.

Postoperatively, she continued to bleed a large amount through the chest tubes, developed a large hematoma on the anterior chest wall, and was given large volumes of blood by transfusion. On the 2nd day, she became jaundiced and oliguric and was treated intensively medically, but the jaundice increased and the oliguria persisted. Studies for a possible transfusion reaction were negative. Blood culture was negative. Remaining deeply jaundiced and oliguric, she gradually deteriorated, terminally had cardiac arrest, and died 4 days after surgery, and 12 days after admission to the hospital.

Necropsy Findings:

1. Pulmonary stenosis, infundibular and valvular types, operated.
2. Atrial septal defect at fossa ovalis, operated.
3. Hemothorax: left, 700 cc; right, 200 cc.
4. Organizing pericarditis.
5. Myocardial necrosis.
6. Fat embolization to kidneys.
7. Extreme acute passive congestion of the liver.
8. Atelectasis of left lung.
9. Passive congestion of right lung.
10. Hematoma of anterior chest wall, extensive.
11. Hydropic degeneration of renal tubes.
12. Acute hemorrhagic focal necrosis of the frontal, occipital, and temporal lobes of the right side of the brain.
13. Fat embolization to white matter of brain.

SUMMARY OF CASE 713

History: This 13-year-old Hawaiian-Japanese boy entered the hospital for elective cardiac surgery.

Since the age of 5, he had been known to have a heart murmur, and had occasional episodes of dyspnea and cyanosis with squatting.

At the age of 11, 2 years before the final hospital admission, cardiac catheterizaton was done elsewhere, showing an interventricular septal defect, patent ductus arteriosus, pulmonary hypertension, and a bidirectional shunt.

Physical Examination: He was well nourished and not jaundiced. Weight was 103 lb and blood pressure was 130/80. There was a harsh systolic murmur and mild cyanosis of the extremities. There was no abdominal mass or tenderness.

Clinical Course: Cardiac catheterization with angiocardiography was done under local anesthesia, giving the findings of interventricular septal defect, bidirectional shunt, valvular and infundibular pulmonic stenosis, anomalous right upper pulmonary venous drainage into the superior vena cava, and a patent foramen ovale or an interatrial septal defect. A patent ductus arteriosus was not demonstrated.

Nine days after admission, he underwent surgery consisting of total cardiopulmonary bypass on a heart-lung machine with hypothermia, including repair of an interventricular septal defect, infundibular resection, pulmonary valvulotomy, and plastic reconstruction of the right ventricular outflow tract with an Ivalon patch, with implantation of a cardiac pacemaker. He was found to have tetralogy of Fallot with infundibular and valvular pulmonary stenosis, anomalous right upper pulmonary venous drainage, and a patent foramen ovale.

Postoperatively, on the 1st day, he was in complete heart block, had fever, and was treated with the cooling blanket. On the 2nd day, he suddenly and unexpectedly had cardiac arrest, which failed to respond to external cardiac massage. He was never jaundiced, and died 2 days after surgery, and 11 days after admission to the hospital.

Necropsy Findings:

1. Tetralogy of Fallot (surgically treated).
2. Patent ductus arteriosus.
3. Partial anomalous connection, right upper pulmonary vein to superior vena cava.
4. Atrial septal defect.
5. Atelectasis, lower lobes.
6. Hydropic change in the proximal convoluted tubules of the kidney.
7. Silicone emboli in the kidneys.
8. Hemothorax, right, 200 cc.

SUMMARY OF CASE 716

History: This 58-year-old white man entered the hospital for an elective Whipple operation.

During the year preceding the final admission, he had a 20-lb weight loss. Some 6 months before the final admission, painless jaundice gradually developed.

Three months before the final admission, a laparotomy was performed elsewhere, and adenocarcinoma involving the ampulla of Vater, with extension to the pancreas, was found. A cholecystoduodenostomy was done and the jaundice cleared. He was eventually admitted for elective surgery.

Physical Examination: He was thin and not jaundiced. Blood pressure was 150/90. There was no abdominal mass or tenderness.

Clinical Course: Three days after admission, a very extensive operation lasting 11 hr was performed, including a modified Whipple, resection of the transverse colon, vagotomy, cecostomy, and ligation of the splenic artery without splenectomy. Carcinoma involving the ampulla of Vater, the local lymph nodes, the omentum, the head of the pancreas, and the cholecystoduodenal anastomosis was diagnosed.

On the night of surgery he had a satisfactory urine volume, but on the morning of the 1st day, he was found to be anuric and to have marked hemolysis, with a fall in PCV as low as 2, a fall in total hemoglobin as low as 6.4, a fall in RBC hemoglobin as low as 6.0 g percent, and a rise in plasma hemoglobin to 5.8 g percent. A transfusion reaction was diagnosed initially, but not proved. He was thought to have septicemia, probably clostridial. He had fever from 103.8 down to 96 F, became jaundiced (an orange-red hue), and was treated with an exchange transfusion, antibiotics, steroids, and gas gangrene antitoxin. He remained anuric and died 2 days after surgery, and 5 days after admission to the hospital.

Necropsy Findings:

1. Massive hemolysis due to Clostridium perfringens.
2. Massive infarction of the spleen due to interruption of the splenic artery.
3. Infarcts of the liver.
4. Abscess, peripancreatic, due to Clostridium perfringens.
5. Pulmonary edema.
6. Acute renal tubular degeneration.
7. Hemorrhagic effusions of all serous cavities: right pleura, 800 to 1000 cc; left pleura, 800 to 1000 cc; peritoneum, 1500 cc; and pericardium, 20 cc.
8. Degeneration of heart muscle.
9. Mild cholestasis and portal fibrosis.
10. Congenital cysts of the liver.
11. Culture of the purulent material about the pancreas at necropsy grew Clostridium perfringens, a Klebsiella species, and intermediate coliform organism, alpha-hemolytic streptococci, and an Alcaligenes species.
12. Culture of the free peritoneal fluid at necropsy grew Clostridium perfringens, E. coli, and alpha-hemolytic streptococci.

SUMMARY OF CASE 717

History: This 66-year-old white man entered the hospital for evaluation of arterial insufficiency in his legs.

Arteriosclerotic heart disease was prevalent for 5 years. Five years before the final admission, he had had a myocardial infarction, and he had been on digitalis since then.

For 2 years, he had had intermittent claudication in the left leg, with pain in the gluteal area, thigh, and calf, but particularly the gluteal area, coming on with walking one block.

Two months before the final admission, he was hospitalized elsewhere with pneumonia, and was found to have a right pleural effusion.

Physical Examination: He was well nourished and not jaundiced. Blood pressure was 130/70. He had signs of a right pleural effusion. There was no abdominal mass or tenderness. The left femoral, popliteal, posterior tibial, and dorsal pedal pulses were absent, whereas the pulses on the right were strong.

Clinical Course: Chest x-rays showed a right pleural effusion. Thoracentesis produced 750 cc of fluid, which was negative for malignant cells. An aortogram showed complete obstruction of the left iliac artery, and a left femoral arteriogram showed that the common, superficial, and deep femoral arteries were patent.

Nine days after admission he was to have surgery, but an attempted epidural anesthesia became subdural, so no procedure was done.

Fourteen days after admission, or 5 days after the original attempted anesthesia, he underwent placement of a Teflon graft from the aorta to the left common femoral artery. During this procedure, there was some difficulty with clotting and with establishment of flow.

After this, the pulses became weaker and disappeared, and the left leg became cool and pale. Five hours after the first operation, he had a second operation, which was re-exploration of the graft, with removal of clot and retrograde flushing through an incision in the posterior tibial artery. Immediately after this operation, the pulses were good, but within 4 hr the left leg was cold and pale. He was then treated with caudal anesthesia and heparin. Over the next 2 weeks, pain and gangrene developed in the left lower extremity and 23 days after operations 1 and 2, operation 3 was done: a left above-the-knee amputation.

One day postoperatively, he developed marked chest pain, a pulmonary embolism was diagnosed, and he was treated with heparin. On the 2nd day, he again had severe chest pain, his liver was enlarged to 6 cm below the costal margin, and he showed signs of pulmonary congestion. He was never jaundiced and was not hypotensive terminally. He died 2 days after operation 3, 25 days after operations 1 and 2, and 39 days after admission to the hospital.

Necropsy Findings:

1. Arteriosclerotic heart disease.
2. Acute coronary thrombosis due to arteriosclerosis.
3. Generalized arteriosclerosis obliterans.
4. Arteriosclerotic heart disease with old and recent myocardial infarction.
5. Congestive heart failure secondary to arteriosclerotic heart disease.
6. Cerebral arteriosclerosis.
7. Aneurysm of the left common iliac artery.

SUMMARY OF CASE 718

History: This 47-year-old white man entered the hospital because of trouble in swallowing for 6 weeks.

He gave a history of food sticking low in his chest for 6 weeks before the final admission. He had been able to take only fluids and had lost 60 to 70 lb. X-rays had shown "cardiospasm." There was no history suggestive of an ulcer. An attempt to pass a tube into the stomach had been unsuccessful.

Six months before the final admission, he had been hospitalized for 4 days with an alleged myocardial infarction, and had been taking digitalis since then.

Diabetes was known for 4 years, and he was taking 50 units of NPH insulin per day.

Physical Examination: He was thin and not jaundiced. Weight was 127 lb. Blood pressure was 150/80. There was no abdominal mass or tenderness.

Clinical Course: X-rays showed a large carcinoma involving almost all of the stomach and the lower 3 to 4 cm of the esophagus. Nine days after admission, after preparation with antibiotics, an extensive 9-hr operation was performed, including a total gastrectomy, splenectomy, resection of the tail of the pancreas, resection of 5 to 6 cm of the esophagus, with esophagojejunostomy, jejunojejunostomy, and a feeding jejunostomy.

Postoperatively, he had fever, pneumonia, and suspected pulmonary embolism or myocardial infarction, developed a fluid collection in the right chest, was shown by administration of Congo red to have leakage from the anastomosis, had placement of several tubes in the abdomen and in the chest under local anesthesia, and was demonstrated by x-ray to have leakage from the anastomosis. He was hypotensive for the last 3 days of life, requiring vasopressors and blood. He was never jaundiced, gradually deteriorated, and died 11 days after surgery, and 20 days after admission to the hospital.

Necropsy Findings:

1. Extensive infarcts, parenchymal necrosis, lobular atrophy, metastatic adenocarcinoma, and passive congestion of the liver.
2. Pleural scarring, atelectasis, multiple lung abscesses, and scattered pneumonia.
3. Breakdown of the esophagojejunal anastomosis, with resulting leak and loculation of mucopurulent material at the site of the anastomosis and with about 700 cc of serosanguineous fluid in the left pleural cavity.
4. Pericarditis.
5. Peritonitis.
6. Metastatic carcinoma to omentum and para-aortic lymph nodes.
7. Generalized arteriosclerosis.
8. Acute mucosal ulcerations of the esophagus.
9. Submucosal necrosis and hemorrhage of the colon.

SUMMARY OF CASE 719

History: This 62-year-old white woman entered the hospital for the seventh time for the treatment of her ulcerative colitis.

She had been followed in the same clinic for 4 years with preoperative diagnoses thought to be rheumatoid arthritis, Alzheimer's disease (central-nervous-system disease), chronic constipation, hemorrhoids, and chronic anemia.

Four years before the final admission, a hemorrhoidectomy was performed under general anesthesia. The tissue removed at this time showed nonspecific granuloma. She was allegedly incontinent of feces from this time onward. At that hospitalization, the total protein was 6.8; albumin, 3.9; and globulin, 2.9. Review of all the records reveals no other tests pertaining to the liver.

Two and one-half years before the final admission, she was admitted for "anal stenosis" and underwent a posterior anotomy and a limited hemorrhoidectomy. This second operation was also performed under general anesthesia.

One year before the final admission, she was admitted for evaluation of her diarrhea, rectal bleeding, and alleged incontinence of feces. Barium enema at this time was negative. She was thought to have subacute ulcerative colitis and was started on medical treatment, the details of which are unknown.

During this time she had had several other hospitalizations for psychosis and Alzheimer's disease, but there was never complete agreement as to the nature of the central-nervous-system disease.

She was admitted finally with a history of 15 to 20 bowel movements a day, with rectal bleeding and passage of mucus by rectum for 2.5 years. Recent barium enema and proctoscopy had shown the changes of ulcerative colitis. During this time her muscle weakness, ataxia, sensory loss, and memory loss had waxed and waned.

Physical Examination: She was poorly nourished (weight, 90 lb), appeared chronically ill, and was not jaundiced. Blood pressure was 120/70. The liver was palpable three fingerbreadths below the right costal margin and was tender. There was poorly localized right lower quadrant tenderness. There was decreased sensation over both lower extremities.

Clinical Course: X-rays again confirmed ulcerative colitis. She was thought this time to have polyneuropathy, rather than Alzheimer's disease.

Eight days after admission, a total colectomy, including abdominal-perineal resection of the rectum, with an ileostomy was performed. The

specimen showed ulcerative colitis with pseudopolyposis and an ulcer completely surrounding the ileocecal valve. Postoperatively, she did well and her ileostomy was functioning until the 7th day, when she developed abdominal cramps and distention.

Eight days after the first operation, operation 2 was performed: a laparotomy for a small bowel obstruction. She was found to have volvulus of the small intestine around the ileostomy in the gutter, which had not been closed. The volvulus was reduced and the gutter closed, and no resection was necessary.

From the time of operation 2, marked right upper quadrant tenderness developed, and a closed-loop obstruction or a loop of gangrenous intestine was diagnosed. Accordingly, 3 days after operation 2, she underwent operation 3, exploration of the right upper quadrant under local anesthesia, in which serosanguineous fluid was found, but no abscess or obstructed or gangrenous loop.

After operation 3, she remained oliguric and hypotensive and developed twitching, and then gross bleeding through the nasogastric tube and from the right lower quadrant drain. She developed convulsions, gradually deteriorated, was never jaundiced, and died 5 days after operation 3, 8 days after operation 2, 16 days after operation 1, and 24 days after admission to the hospital.

Necropsy Findings:

1. Pseudomembranous colitis.
2. Fibrinopurulent peritonitis.
3. Infarction of the liver (no comment in necropsy report about hepatic artery).
4. Atelectasis of both lungs.
5. Bronchopneumonia.
6. Renal tubular necrosis.
7. "Alzheimer II changes" described in the brain (no other diagnosis made concerning brain).

SUMMARY OF CASE 723

History: This 62-year-old white man entered the hospital because of gradual deterioration for 1 year, with pain in both legs and hips.

He had been admitted 5 years before the final admission with symptoms of urinary obstruction and pain in his back. Cystoscopy and biopsy of the prostate showed carcinoma of the prostate. X-rays showed metastases to the pelvis. There was no abdominal mass or tenderness. He underwent bilateral orchiectomy and was started on stilbestrol. Laboratory findings at that time were: hemoglobin, 11.7; RBC, 3.89 million; WBC, 7200; platelets, 139,000; sedimentation rate, 115; blood sugar, 101; acid phosphatase, 2.8; alkaline phosphatase, 4.9; total protein, 6.9; albumin, 4.2; globulin, 2.7; and NPN, 43.

Two years before final hospitalization, he was admitted for 3 days with the complaint of pain in his hip. At that time, he was still taking stilbestrol, 50 mg three times a day, and Meticorten, 5 mg three times a day. He had no abdominal mass or tenderness. X-rays showed very extensive metastases. Cystoscopy showed no change, and he was advised to continue his medications. Laboratory findings that time were: hemoglobin, 12.2; RBC, 3.89 million; WBC, 10,800; sedimentation rate, 16; alkaline phosphatase, 6.3; and acid phosphatase, 0.80.

Because of gradual deterioration, pain in his hips and legs, and a 30-lb weight loss, he was admitted finally. He had become anemic and had had multiple blood transfusions, the number and timing of which are not known. It is known, however, that he received 1000 cc of blood 2 months before the final admission.

Physical Examination: He was emaciated (weight, 116 lb), appeared chronically ill, and was not jaundiced. Blood pressure was 100/70. There was bilateral gynecomastia. The liver was enlarged to percussion, although the size was never accurately determined. The liver was also described as "palpable and tender." He had numerous ecchymoses, and enlarged lymph nodes in both inguinal regions. The prostate was markedly enlarged and hard and was almost totally obstructing the rectum.

Clinical Course: X-rays showed numerous bony metastases. He was studied and prepared with drugs and then, 13 days after admission, underwent hypophysectomy by the trans-antral transsphenoidal route.

Postoperatively, he never improved remarkably, but continued to have thrombocytopenic purpura, gradually became weaker, and was treated with steroids, stilbestrol, thyroid, blood, and antibiotics. On the 23rd day, his temperature rose to 104 F, he developed jaundice and dark urine, and the liver became tender and enlarged to five fingerbreadths below the right costal margin. Remaining jaundiced, he became confused and disoriented and was thought to be in hepatic coma, but did not show liver flap. At this time, it was determined that he had had transfusion 3 months previously and he was thought to have serum hepatitis or liver metastases. A lumbar puncture was negative. He remained jaundiced, gradually deteriorated, and died 42 days after surgery, and 55 days after admission to the hospital.

Necropsy Findings:

1. Adenocarcinoma of the prostate with local extension to the seminal vesicles, involvement of supraclavicular, hilar, lumbar, para-aortic, iliac, femoral, and inguinal lymph nodes, and subpleural lymphatics; metastases to liver, both adrenals, and cranial dura mater; extensive bony metastases and replacement of vertebral, sternal, and costal bone marrow with secondary anemia, thrombocytopenia, and cutaneous purpura.

2. Bilateral hydrothorax, marked, 1500 cc.
3. Partial atelectasis of lower lobes of lungs.
4. Ascites, 500 cc.
5. Chronic passive congestion of the liver and central hemorrhagic necrosis, marked.
6. Organizing pneumonitis, left lower lobe.
7. Extramedullary hematopoiesis in spleen and liver.
8. Metastatic carcinoma in cerebral dura, left cavernous sinus, mucous membrane of the sphenoid sinus, and sphenoid bone.
9. Acute and chronic sphenoid sinusitis, left.
10. Acute and chronic osteomyelitis, mild, localized, in bony septum of sphenoid sinus.
11. No residual pituitary tissue found in the sella turcica post mortem.

Comments by Pathologist: "Necropsy disclosed widespread malignancy and a constellation of anatomical lesions which indicated congestive heart failure. One component of the latter condition, that is, central hemorrhagic necrosis of the liver, is considered to be the cause of jaundice in this case."

SUMMARY OF CASE 724

History: This 33-year-old white woman reentered the hospital for repeat elective cardiac surgery.

She had no definite history of rheumatic fever, but had had scarlet fever and many sore throats as a child.

Two heart murmurs had been known since her first pregnancy, 11 years before the final admission.

Nine months before the final admission, angiocardiography showed mitral stenosis, mitral insufficiency, and pulmonary hypertension. At that time, she had had a closed mitral valvulotomy under general anesthesia and was found to have severe disease of the mitral valve with considerable mitral insufficiency. It was felt that little was accomplished and that she needed later surgery with opening of the heart with use of a heart-lung machine.

Three months before final hospitalization, she was admitted for 3 days for evaluation. Nothing specific was done at that time. The liver was not palpable at that admission.

In the interim preceding the final admission, no improvement was noted. She had pneumonia treated with an unknown antibiotic, and an increasing dyspnea on exertion. Digitalis, potassium chloride, Diuril, and sulfadiazine were the medications taken. The liver was described as palpable four to five fingerbreadths below the right costal margin, but not tender, on two examinations in the clinic. This is the only time the liver had been noted to be enlarged.

Physical Examination: She was thin, not cyanotic, and not jaundiced. Pulse was 100 and absolutely irregular. Blood pressure was 110/70. There were systolic and diastolic heart murmurs and signs of cardiac enlargement and atrial fibrillation; there was no abdominal mass or tenderness, and no sign of congestive heart failure.

Clinical Course: Seven days after admission, she underwent a procedure for valvulotomy and plastic correction of the insufficiency of the mitral valve with a Teflon patch, including total cardiopulmonary bypass on a heart-lung machine. It was felt that the repair was completely unsatisfactory and that increased mitral insufficiency had been produced. The operation was terminated because of a tear in the atrium, with bleeding that was never completely controlled.

Postoperatively, she continued to bleed through her chest tube and developed cyanosis, signs of pulmonary edema, and a left hemothorax. She became oliguric and hypotensive, gradually deteriorated, was never jaundiced, and died 4 days after surgery, and 11 days after admission to the hospital.

Necropsy Findings:

1. Rheumatic mitral valvulitis with mitral stenosis and insufficiency.
2. Cardiac hypertrophy.
3. Congestive heart failure.
4. Hemothorax, left, 900 cc.
5. Infarction of left and right ventricles, massive, acute.
6. Cardiac dilatation.
7. Embolization of glomerular capillaries, cause undetermined (? silicone from antifoam chamber of the pump oxygenator).

SUMMARY OF CASE 802

History: This 65-year-old white man was admitted to the hospital because of vomiting of blood.

The patient was not able to give an accurate history, but the history was obtained from a friend that he had had vague abdominal pain for 3 weeks. There was no history of gastrointestinal bleeding or abdominal pain previously. He was admitted because of 1-day vomiting of dark blood, followed by vomiting of bright red blood, and then passage of dark blood by rectum.

He "used to drink fairly heavily," but admitted to less than a half-pint of whiskey per day. It appears likely that he used more alcohol than this, because he had alcohol on his breath when he was admitted and because the hospital records show that he had been brought to the hospital twice in the hands of the police for minor injuries.

One month before the final hospital admission, he had had an injection of cortisone for arthritis.

Physical Examination: He was obese, acutely ill, drowsy, and confused, and had alcohol on his breath. He was not jaundiced. Pulse was 80 and

blood pressure was 150/60. There was no abdominal mass or tenderness and no spider angiomata.

Clinical Course: He was given blood and stopped bleeding, but then restarted. He was then treated with a very large amount of blood with a Blakemore-Sengstaken tube. Continuing to bleed in spite of intensive drug and massive blood administration, he was taken to surgery for an emergency operation 1 day after admission.

This operation was an exploratory laparotomy with two gastrotomies, ligation of a single large bleeding gastric varix, and a side-to-side portacaval shunt, with good reduction in the portal pressure.

Postoperatively, he was hypotensive and confused, and continued to bleed both through the nasogastric tube and by rectum. He was given large amounts of blood and again treated with the Blakemore-Sengstaken tube. He was never described as jaundiced, but probably was jaundiced for the last 2 days of life, as indicated by the bilirubin (up to 6.6). Gradually deteriorating, he died 2 days after surgery, and 3 days after admission to the hospital.

Necropsy Findings:

1. Arteriosclerotic heart disease.
2. Postnecrotic cirrhosis, with superimposed hepatoma.
3. Esophageal, gastroduodenal, and gastric varices with multiple bleeding points.
4. Portacaval anastomosis intact and apparently functioning as seen at necropsy.

SUMMARY OF CASE 807

History: This 57-year-old white man, a farmer, entered the hospital because of a 1-month history of steadily increasing chest pain and loss of appetite.

There was a history of a "high alcoholic intake," but no further details were available on this point.

Physical Examination: He was thin, appeared chronically ill, and was not jaundiced. Blood pressure was 125/80. There were decreased motion and decreased breath sounds over the left lung. There was no abdominal mass or tenderness.

Clinical Course: Chest films showed a lesion in the left lung, which was probably a carcinoma. A single sputum was positive for acid-fast bacilli, but numerous other sputums were negative. Bronchoscopy under local anesthesia showed a lesion in the left lower lobe, which was biopsied and shown to be a squamous cell carcinoma.

Fourteen days after admission, he underwent a left pneumonectomy for what was shown to be a squamous cell carcinoma of the left lower lobe, adherent to the chest wall, with central abscess formation.

Postoperatively, he did well until the 3rd day, when he was transiently hypotensive but responded to 500 cc of blood. After this, he did well until the 12th day, when he suddenly became cyanotic and hypotensive; but he improved when his left chest was tapped and a small amount of air was released. A bronchogram done then showed no leakage from the bronchial stump. He died suddenly 13 days after surgery, and 27 days after admission to the hospital. He was never jaundiced.

Necropsy Findings:

1. Bilateral hemothorax (1800 cc clotted blood, left pleural cavity; 300 cc clotted blood, right pleural cavity).
2. Acute and partially organized sanguinofibrinous pericarditis (80 cc, E. coli cultured at necropsy).
3. Congestion and edema of the right lung, moderate, 920 g.
4. Acute tracheobronchitis.
5. Acute congestion of the liver, advanced, with central lobular necrosis.
6. Acute congestion of the spleen and kidneys, moderate.

SUMMARY OF CASE 812

History: This 65-year-old white man, an itinerant unemployed handyman and chronic alcoholic, entered the hospital for the fourth time, 5 days after his most recent discharge from this hospital, because of fever.

Three years before the final admission, he was hospitalized for 25 days with pneumonia of the right lower lobe. At that time he was not jaundiced and the liver was not enlarged. Bronchoscopy under local anesthesia showed narrowing of the left lower lobe orifice. He was treated with penicillin and Achromycin, and was also diagnosed as having "probable Laennec's cirrhosis," based on laboratory findings. Laboratory findings were: hemoglobin, 10; PCV, 35; WBC, 23,300; prothrombin time, 35 percent; NPN; 36; blood sugar, 89; total protein, 6.5; albumin, 3.0; globulin, 3.5; thymol turbidity, 6.5, 10; cephalin flocculation, 2-3+ in 24 hr, 4+ in 48 hr; alkaline phosphatase, 4.1; bilirubin, total 0.8, direct 0.5, indirect 0.3; and BSP retention, less than 5 percent.

One year before the final admission, he was admitted for the second time for 21 days with severe pneumonia of the left lower lobe and left upper lobe, plus congestive heart failure. Bronchoscopy under local anesthesia showed narrowing of the right upper lobe orifice. The liver was enlarged to five fingerbreadths below the right costal margin and was slightly tender. He was not jaundiced and was treated with digitalis, penicillin, Chloromycetin, and streptomycin. Representative laboratory findings at that time were: hemoglobin, 13; PCV, 37; WBC, 23,000; BUN, 82, later 26; creatinine, 2.2; blood sugar, 124; total protein, 6.3; albumin, 3.9; globulin, 2.4; bilirubin, total 0.5,

direct 0.3, indirect 0.2; and BSP retention, less than 5 percent.

Forty days before the final hospital admission, he was admitted for a third time for 45 days. At that time, he entered with a 2.5-week history of chills, fever to 102 F, anorexia, and polydipsia, and was found to have signs of emphysema and enlarged lymph nodes in the neck, axilla, and inguinal region. The liver was found 5 fingerbreadths below the right costal margin. A right axillary and supraclavicular lymph node biopsy, which was done under local anesthesia, gave the diagnosis of Hodgkin's lymphoma. He was treated with nitrogen mustard, 0.1 mg/kg twice and 0.2 mg/kg once. This was followed by a fall in the WBC and PCV, but no improvement. He was then treated with prednisone, 15 and later 10 mg four times a day, with improvement. Representative laboratory findings at that time were: hemoglobin, 13, later 9.5; PCV, 42, later 30; WBC, 5300, later 420, later 11,500; platelets, 407,000; BUN, 16; blood sugar, 87; total protein, 8.0; albumin, 5.0; globulin, 3.0; thymol turbidity, 4.1; alkaline phosphatase, 3.5; bilirubin, total 0.5, direct 0.3, indirect 0.2; and uric acid, 2.9.

After his most recent discharge, he had been home for 5 days, and for 3 days had no fever, but had had fever and sweating for 2 days. He had been taking prednisone, 10 mg three times a day.

Physical Examination: He was obese (weight, 180 lb), chronically ill, and sweating, but not jaundiced. Temperature was 103 F and blood pressure was 130/70. There were enlarged lymph nodes in the neck and inguinal regions. The liver was two fingerbreadths below the right costal margin and was not described as tender. The spleen was not palpable.

Clinical Course: He was treated with steroids and then Vincaleukoblastine, but continued to have fever. His bone marrow became depressed and he was treated with antibiotics.

On the 36th day, he was found to be hypotensive to 70/40, to be passing blood by rectum, and to return bright red blood from his nasogastric tube. He continued to bleed in spite of transfusion.

Accordingly, on the 36th day, he underwent an exploratory laparotomy, in which he was found to have bleeding from multiple superficial ulcers throughout the stomach. The procedure included a sixty percent subtotal gastrectomy, with gastrojejunostomy, and suture-ligature of ulcers remaining in the retained portion of the stomach.

After this operation, he was comatose with fever as high as 104 F. He went into congestive heart failure, was thought to be suffering from over-transfusion, had two phlebotomies, and was treated intensively medically. He remained comatose, had serosanguineous drainage from his incision, and was thought to have had dehiscence of the fascial portion of the incision. Continuing to bleed by rectum, he had increasing respiratory distress, was thought to show signs of pneumonia, gradually deteriorated, was not hypotensive, was never jaundiced, and died 6 days after surgery, and 42 days after admission to the hospital.

Necropsy Findings:

1. Hodgkin's disease, granulomatous type with lymphadenopathy, systemic, involving mediastinal, periaortic, cervical, and mesenteric lymph nodes, with splenomegaly, 490 g.
2. Bronchopneumonia, acute and organizing, massive, bilateral, with congestion and edema, massive, of lungs.
3. Ulcerations, acute, superficial, small, multiple, mucosal, of remaining portion of stomach.
4. Bleeding, massive, recent, gastrointestinal tract.
5. Hemoperitoneum, recent, localized to site of operation, 400 cc.
6. Valvulitis, rheumatic, healed, of mitral and aortic valve, with mitral stenosis, slight, cardiomegaly (500 g), ulcerations, superficial, multiple of the mitral valve, and vegetations, nonbacterial, small, multiple, on the mitral valve.
7. Chronic passive congestion, marked, of liver, with central necrosis.
8. No gross involvement of the liver by Hodgkin's disease.

SUMMARY OF CASE 824

History: This 10-year-old white girl entered the hospital for elective cardiac surgery.

She had been known to have a heart murmur since birth, with no significant symptoms.

Four years before the final admission, she had had cardiac catheterization, which showed interventricular septal defect and pulmonic stenosis. The liver was not palpable at this admission.

She was admitted finally for elective cardiac surgery, with a history only of slight easy fatigue and slight dyspnea on exertion, and no history of cyanosis or congestive heart failure.

Physical Examination: She was well nourished (weight, 64 lb), not cyanotic, and not jaundiced. Blood pressure was 120/70. There was a systolic murmur. There was no abdominal mass or tenderness.

Clinical Course: Six days after admission she underwent an open-heart operation, consisting of attempted closure of an interventricular septal defect by suturing over it a flap consisting of a pulmonary valve leaflet, pulmonary valvulotomy, and plastic reconstruction of the right ventricular outflow tract, with a Teflon patch. This was performed with total cardiopulmonary bypass on a heart-lung machine. There were two attempts at the enlargement of the right ventricular outflow tract, and the pump time in two runs was a total of 82 min.

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Postoperatively she was slightly cyanotic, but not hypotensive, and initially oliguric. She was in and out of complete heart block and was on a pacemaker.

On the 1st day, she became oliguric, with urine volumes under 100 cc per 24 hr. From the 2nd day onward, she had convulsions, first right-sided, then left-sided, and then generalized. She became unresponsive and showed hemiplegia. She remained oliguric and had bloody urine and marked fluid and electrolyte imbalance. She was hypotensive only for the last hour of life. She was never jaundiced. She died 3 days after surgery, and 9 days after admission to the hospital.

Necropsy Findings:

1. Congenital heart disease with pulmonary stenosis, valvular and infundibular; interventricular septal defect, membranous, high, large, anterior; bicuspid pulmonary valve; right ventricular hypertrophy; operated, with significant right ventricular outflow tract obstruction, unintended, entrapment of the chordae tendinae of the tricuspid valve in the sutures for the repair of the interventricular septal defect, and significant incomplete closure of the interventricular septal defect.
2. Recent encephalomalacia, multiple, small, partly hemorrhagic, in cerebral hemispheres and cerebellum.
3. Petechial hemorrhages, recent, diffuse, in cerebrum, cerebellum, and brainstem.
4. Pulmonary hemorrhage, focal ("pump lungs").
5. Acute passive congestion of viscera.
6. Acute passive congestion of liver with central lobular necrosis.
7. Albuminous casts in kidney tubules, extensive.

CHAPTER III-2. REPORT OF THE PATHOLOGY PANEL

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Massive hepatic necrosis was initially selected as the basis for an analysis of halothane toxicity. It seemed reasonable to assume that this condition could be related to universally acceptable criteria and that, when present, it would constitute a sufficiently important lesion to find its way into a necropsy summary or a list of diagnoses. Thus, in each of the 34 participating hospitals a knowledgeable physician ("local selector") reviewed the files of the cases necropsied at his institution during the 4-year period of the Study and selected all those thought to reflect massive hepatic necrosis that occurred within 6 weeks of the administration of a general anesthetic. This survey yielded a total of 184 cases from all institutions; these were gathered from an over-all total of 10,171 complete necropsies.

Later, abstracts of all necropsy reports were resurveyed by another person in a central institution (a nurse-medical librarian), to be certain that no cases of hepatic necrosis had been missed by the local selector. To ensure the inclusion of all possible cases, the reviewer selected all additional cases that were thought to represent massive or even lesser degrees of necrosis or whose necropsy reports mentioned hepatitis. This survey yielded 42 additional cases. The aggregate from the two surveys was therefore 226 cases.

To establish the fact of massive necrosis with reasonable consistency and assurance, a Pathology Panel was convened, consisting of six members with special interest and experience in hepatic disorders. For each of the 226 cases, a complete abstract (lacking only an indication of the anesthetic used), a summary of the necropsy findings, and representative sections of liver were supplied to the Panel.

METHOD OF PATHOLOGY REVIEW

Initially, each member of the Pathology Panel received sections of all 226 livers stemming from this portion of the survey, but with no knowledge of the source or the clinical manifestations. The Panel developed a simple tally form on which were indicated the various histologic features to be evaluated (Pathology Form 1). This tally had two purposes: (1) to determine the nature and extent (or absence) of necrosis, and (2) to permit tabulation of the histologic features that, in aggregate, might constitute a complex with specific implications for halothane or other agents. Thus, parenchymal cellular alteration, autolysis, fatty change, inflammatory exudate, cholestasis, and ductal and ductular peculiarities, and their degree and distribution, were listed and directed the attention of all panelists to common features. It must be emphasized that throughout this and later steps the pathologists did not know which anesthetic had been used in any patient.

EXTENT OF NECROSIS

In examining the liver for necrosis, each Panel member substantiated its existence (or absence) and indicated its degree. The latter was arbitrarily classified as: 1+, minor, not affecting more than 25 percent of the lobular parenchyma; 2+, affecting 25 to 50 percent of the parenchyma; 3+, destruction of approximately 75 percent of the parenchyma; or 4+, massive, affecting all or almost all the parenchyma. No effort was made to delineate the nature or cause of the necrosis during this phase of the study. In a later survey, however, cases that exhibited histologic features attributable to coincidental intrahepatic disorders, such as infarction, abscess, necrotic neoplasm, and alterations related to biliary obstruction, were deleted from further consideration, as were those with autolysis of a degree sufficient to preclude interpretation.

On the cases retained as acceptable examples of hepatic necrosis, there was reasonably close agreement among the evaluators. Variations in scores were usually minor. But it was necessary for the members of the Panel to resolve differences in the relatively few cases at issue. That was accomplished readily, inasmuch as the discrepancies were almost wholly related to a failure, in the course of the preliminary planning, to consider the obscuring factors cited above and those related to pre-existing liver disease. When the differences had been reconciled, the scores were averaged and three categories of necrosis were established: minimal, with an average score of 1.5+ or less (Fig. 1); intermediate, with a score of 1.6 to 2.5+ (Fig. 5); and massive, with a score of 2.6+ or more (Fig. 6).

In the course of determining the terminology to be used at the outset of the study, it was difficult to select phrases that would alert nonpathologist

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screeners at each participating hospital to cases of hepatic necrosis that might be classified by other expressions. These selectors were therefore urged to be lenient in their interpretation of terminology, so that borderline cases would not be missed. Undoubtedly as the result of this, the Panel found it necessary to eliminate 29 of the 226 cases initially received; of these, three were thought to exhibit no evidence of necrosis, seven to be associated with neoplasm, and 19 to be the seat of marked uninterpretable autolysis. Moreover, among the 197 cases retained, 131 were judged to represent minimal necrosis, occasionally barely detectable. Lesions of this type are common in any necropsy population; they constitute a nonspecific reflection of the agonal state and are considered to have negligible significance. These cases were obviously not properly included among bona fide cases as examples of hepatic necrosis, and were therefore deleted. There remained, however, 66 cases: 35 with necrosis of intermediate degree and 31 with massive necrosis (2.6+ or more). This relatively small yield (29 percent) among the cases originally selected for consideration will be discussed further.

SUPPLEMENTARY SELECTION

Experience with selection on the basis of necropsy abstracts suggested that some examples of massive necrosis might have been overlooked by local selectors. It seemed desirable, therefore, to make another effort at screening cases of necrosis that might conceivably have been missed in the first search. This was accomplished by another survey of necropsy protocols. A pathologist* was selected by the Panel and was requested to gather all conceivable examples of hepatic necrosis for final study. In reviewing the 10,171 necropsy reports, it was found that the liver was mentioned in the list of final diagnoses in 5967. The pathologist was asked to consider these carefully and, as in the case of the local selectors, to cull cases whose necropsy reports contained any indication of primary hepatic injury, including hepatitis. Cases of necrosis in relation to metastatic neoplasm, in which there was fatty metamorphosis without necrosis, and in which there was an obvious independent condition (e.g., infarction, abscess, pylephlebitis, obstructive jaundice, alcoholic hepatitis, or other preexisting disease) were not to be included.

On the basis of this survey, 746 additional cases were selected for more detailed evaluation. Histologic preparations were obtained from 720 of these; tissue and sections were not available from the remainder. Two pathologists** at the Armed Forces Institute of Pathology with considerable experience in hepatic disorders reviewed the 720 preparations. They were familiar with the needs of the Study and selected all examples of necrosis, regardless of degree, that were not obscured by autolysis or readily attributable to obvious extrahepatic or intrahepatic cause.

An additional 146 cases of hepatic necrosis were brought to light. Representative sections of these were circulated among members of the Pathology Panel for review, as in the original group of cases submitted. The Panel agreed on the existence of necrosis in all instances. As in the initial survey, the scores rendered were averaged; in 80 there was intermediate necrosis, and in 51 massive necrosis. Most of the remainder represented minimal necrosis and were therefore excluded. The final tally, therefore, combining both the initial screening and the supplementary selection, was 82 cases of massive hepatic necrosis and 115 cases of intermediate hepatic necrosis.

CAUSES OF HEPATIC NECROSIS

At this stage another method of study was carried out with the 226 cases submitted originally by local selectors. Members of the Pathology Panel, who had already reviewed and evaluated the histologic sections, now received abstracts of the clinical course with details of the operative procedure(s), laboratory tests, postoperative course, and findings at necropsy. Again, knowledge of the anesthetic(s) was withheld. From this information and with the knowledge of the histologic features in the liver, another form was completed (Pathology Form 2). This permitted the panelists to indicate their impressions of the causative basis for the hepatic necrosis (i.e., halothane, any hepatotoxin, any drug sensitization, or hepatitis virus; shock, anoxia, or sepsis; any other factor; autolysis; etc.). Unfortunately, in this phase of the study, opinions were greatly individualized and thus showed little uniformity. No pertinent criteria for designating the various etiologic categories had been agreed on in advance by members of the Panel. Each pathologist, therefore, used his own criteria and often found it necessary to designate more than one possible cause. Indeed, it is well recognized that a number of different agents may cause identical hepatic alterations (3, 8, 13). In one category, nonetheless, there was a remarkable degree of conformity: in the group attributed to "shock, anoxia, or sepsis." This group did not, of course, constitute a pathologic entity, but included many overlapping patterns. Moreover, the clinical record made it fairly obvious that one or more of these conditions had prevailed and undoubtedly influenced the pathologist in his conclusion.

PATHOLOGIC FEATURES

Hepatic necrosis has no consistent pattern; all forms and variations may be observed (14). These range from minor focal lesions with either random or regular zonal distribution to total

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parenchymal destruction. Thus, among the cases excluded were those with small collections of neutrophils intermingled with clusters of necrotic liver cells, scattered irregularly, and with no uniform lobular orientation. These occurred frequently, affected considerably less than 25 percent of parenchymal substance, and were deemed of minor import (Fig. 1). They represented the hepatic counterpart of terminal infection or the disintegrative effects of the agonal state.

Another reflection of the metabolic derangements of terminal illnesses and of the postoperative state was the occurrence of fatty vacuolization, which in various degrees might accompany any form of necrosis or indeed appear in marked degree without any necrosis at all (Fig. 2). Such cases were weeded out and excluded because in most instances they represented coincidental concomitants and, although they may have attained considerable prominence, in themselves appeared to have no bearing on the maintenance of hepatic integrity. In a few instances, however, the lesion constituted a significant widespread alteration reflecting severe parenchymal injury (Fig. 3). In these the appearance of the lipid differed somewhat from that unaccompanied by recognizable hepatic cell injury. It exhibited a microvacuolar form causing marked enlargement and irregularity of cells and much architectural disarrangement. Nuclei variously exhibited swelling and pyknosis. Cells underwent cytoplasmic coagulation and necrosis, usually focal; in some there was rather widespread distribution. Paralleling these changes were canalicular bile stasis, neutrophil aggregation, pigment deposit in and undue prominence of Kupffer's cells, and occasionally inflammatory exudate in portal areas. In two cases this pattern had the added feature of "alcoholic hyalin" formation (Fig. 4); both patients were flagrant overusers of alcohol.

In most instances the necrosis was oriented about the centrilobular vein with the extent varying from minimal, or less than 25 percent of the lobule (Fig. 1), to maximal, or more than 75 percent of the lobule (Figs. 5, 6). Total loss of parenchyma (Fig. 7) was rare; the lesions of major degree often showed a thin periportal row of disturbed but viable parenchymal epithelium (Fig. 8). In this group two basic patterns were recognized, but on occasion they appeared to overlap, particularly if of some duration or obscured by postmortem changes.

In one pattern, constituting the result of vascular disturbance and thus characterized by passive congestion, there was dilatation and engorgement of centrilobular veins and the central reaches of hepatic sinusoids (Fig. 9). Seepage of red cells or plasma into the spaces of Disse resulted in attenuation of parenchymal cell plates and ultimately in their necrosis. Cells underwent direct disintegration or exhibited cytoplasmic eosinophilia and nuclear pyknosis. It is probable that these cytologic features merely represented variations of the same process. In those with terminal accentuation of congestion or the later superimposition of another clinical complication (e.g., hemorrhage, shock, or sepsis), cytoplasmic coagulation resulted; in the others, parenchymal attenuation or frank necrosis followed a longer and perhaps more gradual process. Inflammatory cells appeared in moderate numbers, neutrophils predominating in the acute lesion and macrophages in those of longer standing. In cases with sudden and fatal shock, a seeming central pooling of blood and loss of parenchyma were manifest. In this circumstance the linear division between viable and nonviable parenchyma was usually irregular and ill-defined, with contiguous viable cells containing small amounts of lipid. Occasional cells were swollen but exhibited few features of regeneration. The portal areas in these cases were essentially normal.

The other pattern lacked significant evidence of congestion. Here also, however, various components of the lesion exhibited features that appeared to depend in large part on duration. In its most striking form, acute coagulation necrosis of part of or all the lobular parenchyma appeared (Fig. 10). All cells were in an identical state of recent death, characterized by a granular, coagulative shrinkage of cytoplasm with loss or pyknosis of nuclei. A sharp line of separation existed at the juncture with viable elements. Neutrophils were intermingled with the necrotic cells and were aggregated at the zonal margins; various numbers, usually few, were evident in the peripheral viable zone. A rare necrotic cell, sequestered from its neighbors, assumed a hyaline appearance reminiscent of the acidophilic body observed in viral hepatitis (6,11,15). Little fatty change accompanied this lesion and the portal areas were unaffected, except in cases of total parenchymal destruction. In the instances of total or subtotal destruction, the peripheral residuum of parenchyma was the seat of some regenerative activity with swelling and multinuclearity of the parenchymal cells. This was often accompanied by early ductular proliferation.

In still other examples, presumably representing the same lesions but probably with more prolonged courses (or perhaps with long postmortem intervals), cytoplasmic disintegration had occurred, with "fallout" of cells (Fig. 11). The zone of necrosis in these was characterized by a content of granular detritus, fewer or no neutrophils, and an intermingling of macrophages (or Kupffer's cells) filled with bile and hemosiderin pigment. The line of juncture here was not sharp. The residual viable cells now exhibited irregularity, loss of polarity, multinuclearity, and even mitotic activity. At this stage few neutrophils remained. In the more extreme lesions in which the periphery of the lobule was affected, periportal ductular proliferation was striking (Fig. 12). In some of these the portal areas were edematous and contained moderate lymphocytic infiltration. In a few, in both acute coagulative and "fallout" lesions, a very heavy lymphocytic exudate prevailed in the portal areas and was, on occasion, universal in its distribution (Fig. 13).

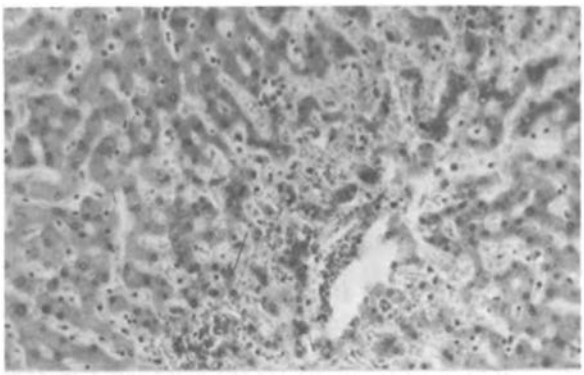

Figure 1.--Minimal centrilobular necrosis (Case 7). Necrosis affects less than 25 percent of the lobular parenchyma. Cells bordering on the centrilobular vein have undergone disintegration and there is dilatation of related sinusoids with a scant intermixture of neutrophils. The remainder of the lobule is intact. Postmortem change affects sharpness of detail. Hematoxylin and eosin. ×150

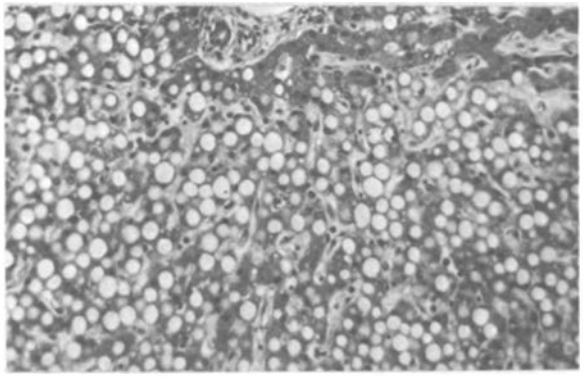

Figure 2.--Fatty liver (Case 105). Liver cells are the seat of severe coarse vacuolization. There is, however, no disarrangement of parenchymal plates and no evidence of accompanying necrosis. A portal area included is quiescent, exhibiting no inflammation. Hematoxylin and eosin. ×150

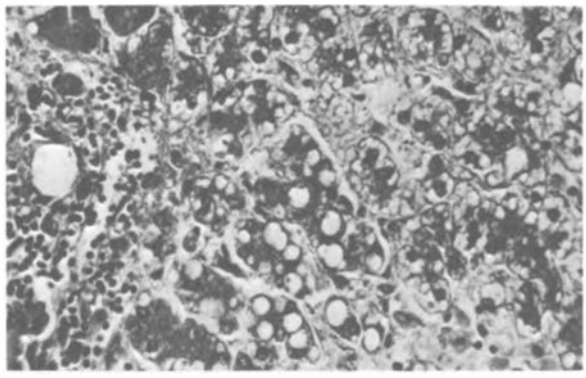

Figure 3.--Toxic hepatitis (Case 206). Severe fatty vacuolization is here characterized by a prevalence of fine foamy cytoplasmic vacuolization with irregularly swollen epithelium. Liver plates are two or more cells thick and elsewhere in this lobule are minute areas of acute necrosis with neutrophil reaction. The portal area included also exhibits a significant inflammatory (lymphocytic) exudate. Hematoxylin and eosin. ×200 (See Fig. 6.)

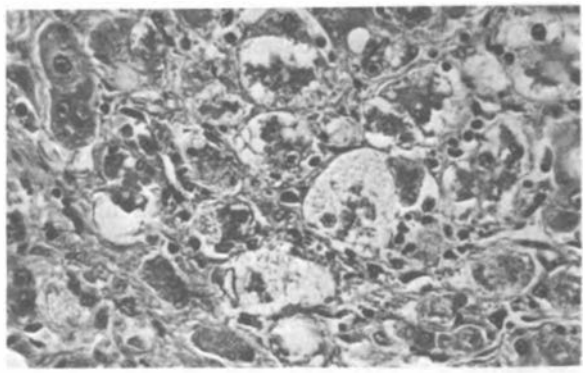

Figure 4.--Alcoholic hepatitis (Case 33). Liver cells are markedly swollen and irregularly disposed and exhibit foci of individual cell necrosis surrounded by a narrow halo of inflammatory cells. Some of the swollen cells appear vacuolated, and others exhibit condensation of cytoplasm to form a refractile eosinophilic coagulum (alcoholic hyalin). Hematoxylin and eosin. ×250

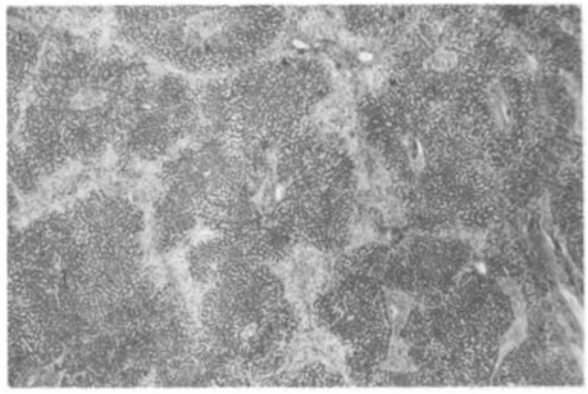

Figure 5.--Intermediate necrosis (Case 200). The central portion of all lobules has undergone necrosis and disintegration. Hematoxylin and eosin. ×100

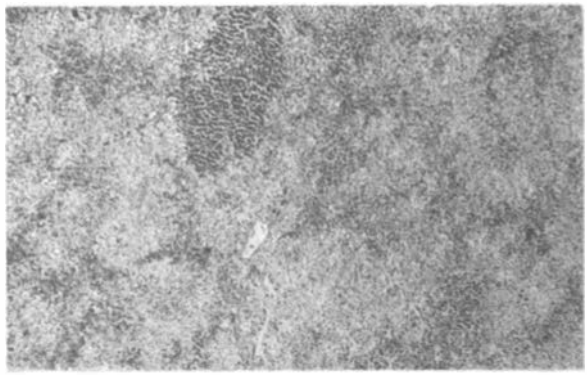

Figure 6.--Massive necrosis (Case 206). Most of the parenchyma has undergone necrosis, with only a few small islands of viable cells remaining. In the main, the necrosis centers about central veins, one of which may be seen in the center of the photograph. Hematoxylin and eosin. ×100 (See Fig. 3.)

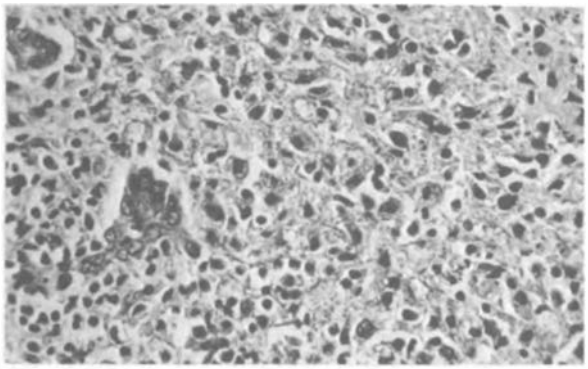

Figure 7.--Massive necrosis (Case 46). Massive necrosis is characterized by complete loss of parenchyma with replacement by detritus, Kupffer's cells, and a mixed inflammatory exudate. At the right is the remnant of a portal area containing interlobular bile ducts and inflammatory cells. Hematoxylin and eosin. ×200

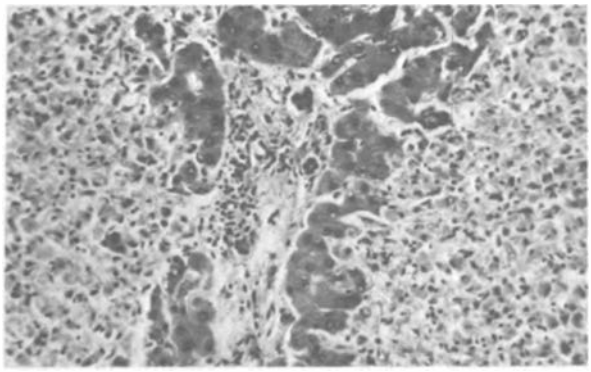

Figure 8.--Massive necrosis, periportal area (Case 36). Almost all the lobular parenchyma has undergone coagulation necrosis and disintegration. A thin rim of viable but abnormal and irregular cells remains, fringing the portal tract. Hematoxylin and eosin. ×150 (See Fig. 18.)

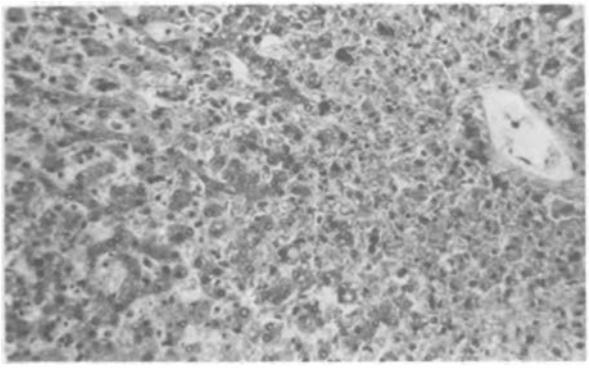

Figure 9.--Intermediate necrosis with centrilobular congestion (Case 82). Centering about the central vein, sinusoids are widely distended by packed red cells, which, because of destruction of approximately one-third of the parenchyma, appear to be pooled. A scant inflammatory reaction appears in the area of destruction. Hematoxylin and eosin. ×150

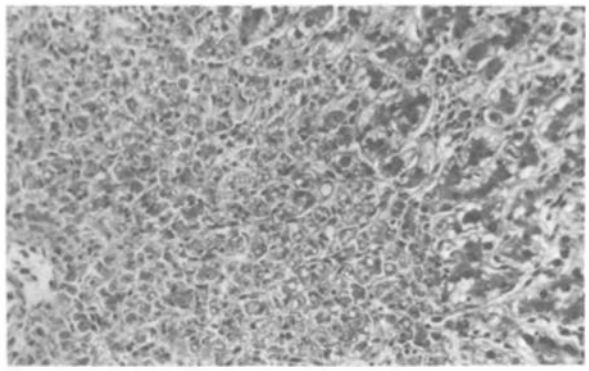

Figure 10.--Centrilobular necrosis (Case 98). Parenchymal cells in the central half of this lobule have undergone coagulation necrosis. Shadowy outlines of the affected cells persist but the cytoplasm has become granular, refractile, and eosinophilic. A few pyknotic nuclei remain but nuclear staining is generally absent. Only a mild early inflammatory reaction is evident at the margin of the necrotic zone. The more peripheral viable parenchyma exhibits cytoplasmic swelling and fatty vacuolization. Hematoxylin and eosin. ×150

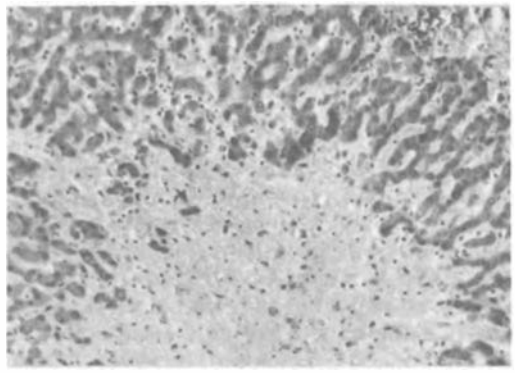

Figure 11.--Intermediate centrilobular necrosis with "fall-out," probably reflecting duration and, perhaps, postmortem interval (Case 86). Necrotic cells have disappeared, leaving behind only an amorphous stromal matrix in which are fragments of nuclear debris and pigment-laden phagocytes. The radial pattern of residual viable cells is undisturbed. Hematoxylin and eosin. ×150

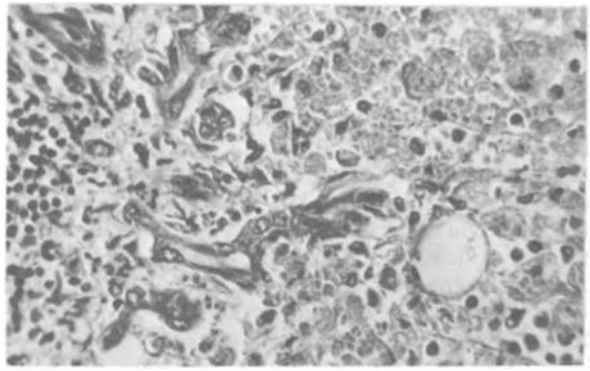

Figure 12.--Massive necrosis (Case 93). Coagulated necrotic cells border on an inflamed portal tract. The few remaining viable elements are swollen, their nuclei are vesicular and bizarre, and there is a ductule-like proliferation. This is thought to represent an abortive effort at regeneration. Hematoxylin and eosin. ×200

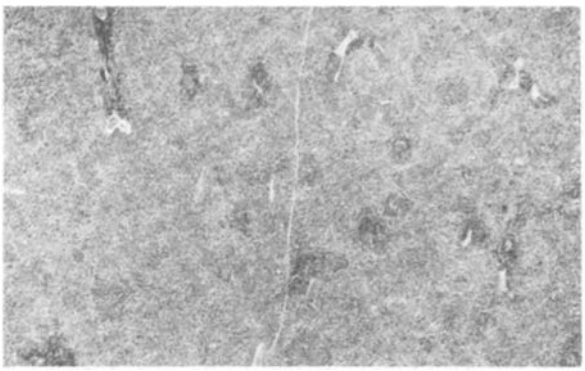

Figure 13.--Massive necrosis (Case 44). Only a few small islands of viable parenchyma remain; the bulk of the liver is necrotic. Each portal area stands out as darkly stained, because of heavy lymphocytic infiltration. There is little inflammation in the parenchymal region. Hematoxylin and eosin. ×100 (See Fig. 19.)

DISCUSSION

The incidence of postoperative hepatic necrosis was relatively modest. The massive lesion appeared in approximately 0.7 percent of necropsy cases, and intermediate necrosis in 1 percent. The minimal lesion was ignored because, as indicated, it is considered to be commonplace in the process of dying and is universally accepted as such. For this reason, its existence might or might not be listed among anatomic diagnoses and its selection by the screener would be unpredictable. This minor degree of alteration, moreover, would not be expected to have significant clinical manifestations or to bear on the outcome of a case. Intermediate necrosis, however, could well contribute to a lethal outcome. Although the Study was not designed to collect cases of this nature, some actually appeared in the first group gathered by local selectors, and others came under consideration in the later collections. Such cases would not, however, be expected to cause death unless associated with another potentially fatal disorder. But massive hepatic necrosis, as defined by the Panel (Figs. 6, 7, 8, and 12), is with very rare exceptions incompatible with life; it is in itself a fatal condition (2,10).

It seems most unlikely that instances of truly massive hepatic necrosis would escape the screening methods used among the necropsy cases. It would have been unusual, indeed, for massive lesions to fail to come to the attention of the local selector, the nurse-medical librarian, and the pathologist examining the necropsy abstracts. It was with this in mind that wide latitude was given the case finders in determining those cases to be subjected to pathologic scrutiny. Such categories as "hepatitis" and "liver degeneration," for example, were therefore included initially, inasmuch as it was intended from the outset to submit sections from all cases to scrutiny by the Pathology Panel. Although some of these did prove to be hepatic necrosis, many were of necessity excluded, and only 31 of the originally collected cases found their way into the final group with massive necrosis.

Nonetheless, in the face of the obvious difficulties in case finding, one may well raise the question of how many examples of hepatic necrosis observed pathologically may have failed to emerge in the diagnostic listings and thus may never have come to the attention of the various screeners. As an additional precaution, the necropsy cases were sampled to detect hepatic abnormality that was not recorded in the final diagnosis. No instances of massive necrosis had failed to be included in the lists of diagnoses in the necropsy protocols examined, although several cases of intermediate necrosis had been missed.

It is reasonable to conclude that almost all examples of massive necrosis in the necropsy population were recognized and examined by the Panel. There is no doubt that there were additional fatal cases with similar lesions among those not necropsied. There is no feasible way of detecting these at present.

Reliability of Coded Diagnosis

A more disturbing matter, however, was the apparent lack of uniformity among pathologists at large in recognizing or designating hepatic necrosis in such a way that it could be appreciated by nonpathologist readers of the pathology reports. The need of the Pathology Panel to reject out of hand 29 of the original 226 cases and to consider 131 others to have only negligible necrosis may in some measure be attributed to typographic errors, the submission of poor or improper sections for review, the manner of performance of necropsies, or the coding of diagnoses by inadequately trained personnel, as well as to the policy adopted of encouraging the local selector to submit questionable cases for evaluation. A review of the abstracts, unfortunately, also indicated a distressing variation in nomenclature and a significant range of pathologic criteria for the diagnosis of necrosis. Among the 226 cases submitted initially, 108 were stated by the local pathologists to have some form of hepatic necrosis and 66 were classified as hepatitis. The submission of the remaining 52 may have represented bias or error, but in most cases undoubtedly reflected an arbitrary choice by the local selector in an effort to avoid missing possible cases of necrosis. They had been listed as fatty infiltration, biliary obstruction, hepatic neoplasm, putrefaction (? autolysis), or pre-existing cirrhosis. However, even among the 108 in which the pathologist's opinion clearly stated that necrosis or hepatitis existed, the Panel found that the lesion could be established as massive necrosis in only 31 cases, and as intermediate necrosis in 35. There was no necrosis in two, necrotic neoplasm in five, and sufficient autolysis to preclude interpretation in 10; in the remaining 25 cases, the necrosis was minimal.

Interpretation of Autolysis

Because it was known that the existence of autolysis would neither exclude nor substantiate the existence of necrosis, the sections and clinical abstracts in 19 cases were evaluated more critically (the 10 originally listed as necrosis by the submitting pathologist and nine considered to represent autolysis but with other features contributing to the selection). So that it could be determined whether necrosis might have been masked by autolysis, the appraisal consisted of a correlation of clinical phenomena and detectable evidence of hepatic necrosis in the poorly stained section (Fig. 14). It appeared reasonable to make this distinction, and in three of the 19 cases hepatic necrosis undoubtedly existed before death. One of these was a patient with choledocholithiasis and biliary obstruction, and another was considered to have had homologous serum hepatitis. The third case, however, could not be explained by the clinical data. The remaining livers, 10 of which had been claimed by the local pathologist to show necrosis, were considered to have been undamaged in life.

Pathologic Alterations Mistaken for Necrosis

A number of cases were listed in necropsy reports as examples of hepatic necrosis but were not so considered by the Panel. The reasons for their exclusion are given below.

In instances of sudden death in healthy persons whose livers were unaffected by degradation before death, the preservation of hepatic parenchymal glycogen, the clarity of cytoplasmic staining, and the sharpness of cell outline all contrast with the usual somewhat blurred "normal" postmortem appearance (Fig. 15). This was, in at least one case, misinterpreted as an abnormality and bears comment only because it was taken as an indication of intrinsic hepatic injury.

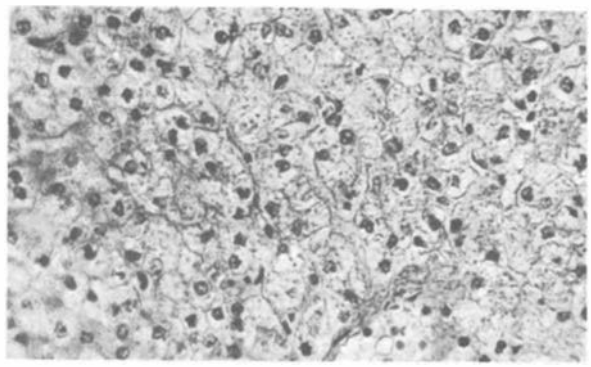

Figure 15.--Normal liver (Case 288). Radiating from the central vein are clearly outlined liver cells with uniform nuclear content. The preservation of the sharp cell membrane is a feature of the liver in sudden death. Hematoxylin and eosin. ×200

The accumulation of parenchymal fat was also considered by some as evidence of hepatic damage. Actually, it is common during a terminal period of illness with restricted caloric and protein intake, and common in the postoperative state as well. Such fatty "degeneration," reflecting reduced protein synthesis (Fig. 2), may be mistaken for toxic hepatitis, which is also characterized by lipid accumulation (Fig. 3) (1,16). Examples of the former complicated by minor evidences of agonal hepatic cellular necrosis, passive congestion, or postmortem parenchymal cell "fallout" seemingly had been misinterpreted as hepatic necrosis, particularly when the fat accumulation was considerable.

A distinction between this form of fatty degeneration and that more commonly associated with toxic injury to the liver, whether following the

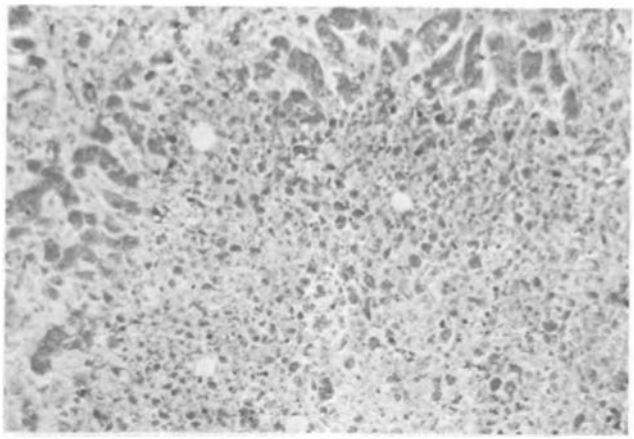

Figure 14.--Autolysis (Case 27). Staining capacity is lost, cytologic detail is obscured, and inflammatory cells cannot be identified. It is still possible, however, to distinguish the centrilobular zone of necrosis from the peripheral fringe of quasi-preservation. Hematoxylin and eosin. ×150

ingestion of noxious agents (as in carbon tetrachloride toxicity) or in the case of acute alcoholism, should be possible in most instances (5). The latter condition was occasionally encountered among the cases with intermediate necrosis. The fuzzy microvacuolar appearance of the lipid (Fig. 3) and its accompanying focal necrosis, bile stasis, neutrophil exudate, and (in the patients with alcoholism) alcoholic hyalin (Fig. 4) constituted clearly distinguishing features. No example of sudden death with simple fatty metamorphosis was encountered.

In a few cases, pre-existing hepatic disorders were improperly related to the postoperative state. Although in some there was evidence of terminal necrosis, this fell into the pattern of chronic hepatitis with portal area inflammation and ductular proliferation but little current parenchymal alteration. Obviously, these had been vulnerable livers and could have been unduly susceptible to vasomotor disturbances. As examples of necrosis induced by anesthetics, however, such cases would have little validity.

Extrahepatic biliary obstruction appeared with the usual manifestations of cholestasis (6) but were often overlain by suppurative complications as well. Whether for this reason or other causes, autolysis was a frequent concomitant, leading in some instances to inclusion in the hepatic necrosis group. In like manner, cases with inflammatory reaction reflecting systemic infection, some with abscess formation (Fig. 16) or advanced autolysis (as with gas bacillus infection), were unjustifiably included. Other conditions encountered were arterial or venous vascular occlusions (some with pylephlebitis), infarction (Fig. 17), and metastatic carcinoma with necrosis of contiguous parenchyma.

Each of these conditions exhibited distinguishing features, and the Pathology Panel felt justified in their exclusion from consideration. Indeed, in almost every instance the manner of death was unrelated to hepatic failure and reflected, instead, another primary disorder.

Figure 16.--Hepatic abscess (Case 214). Case of obstructive jaundice with suppurative cholangitis. Hematoxylin and eosin. × 100

The Panel thus accepted only those cases in which cell death in vivo was recognizable and in which none of the factors indicated above could be incriminated. This constituted the basis for the ultimate selection of the 222 cases.

Hepatic Necrosis Attributable to Anesthetic Agents

Any organ as susceptible to injury by such a wide variety of influences as the liver poses a problem in determining the immediate cause of its malfunction. It is relatively easy (and many have followed this course) to indict an adventitious circumstance in a given instance of hepatic necrosis. But experience has shown that easy assumptions are not particularly fruitful. All attendant conditions require critical evaluation before any single factor can be implicated. This was essentially the situation in patients receiving an anesthetic; they suffered from ailments, serious or not, that required operation, and thereafter they were subjected to the surgical procedure and a host of adjuvant treatments. Each of these provides inherent risks. Moreover, the population at

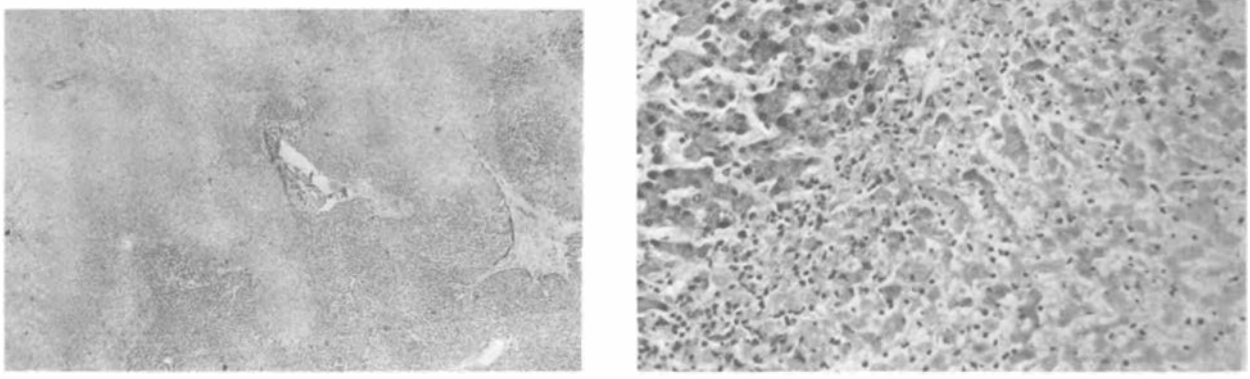

Figure 17.--Hepatic infarct (Case 4). A sharply circumscribed zone of necrosis is brightly eosinophilic and set off from the surviving viable hepatic substance. In the higher-power view (right), the contrast between the cells in the infarct and the viable survivors is well shown. A narrow zone of inflammatory cells encircles the necrotic elements. Hematoxylin and eosin. Left, × 100; right, × 150.

large carries adventitious illness at a certain rate, whether or not manifestations are overt (e.g., viral hepatitis) (4,12,19). Finally, potential risks exist in the anesthetics themselves. Thus, in determining the causal relationships between anesthetics and a group of cases with hepatic necrosis, each case requires individual probing.

The results of a survey carried out by four members of the Subcommittee, representing different medical specialties (anesthesiology, medicine, surgery, and pathology), are recorded in Chapter III-1. That group attempted to determine on the basis of the clinical data available whether the hepatic necrosis could be attributed to factors other than the anesthetic. The group found itself in agreement that the cause of the lesion was apparent in the patient's record in 90 percent of the 197 cases of massive and intermediate necrosis. It would follow that the anesthetic, whatever it proved to be, could well be exonerated in those cases. But there were 19 cases in which all or most of the group did not determine an apparent cause for the necrosis. These were considered "unexplained," as distinct from the "explained" cases in which a clinical basis for the liver destruction was apparent. In these 19 cases, neither the clinical course, the operative procedure, nor the existence of complicating illness appeared to have had the capacity to contribute to the hepatic process.

In nine of the 19 cases the lesion was massive, and in 10 it was intermediate. When decoded as to the anesthetic exposure, it was found that halothane was the agent used in 14 cases (seven massive and seven intermediate), nitrous oxide-barbiturate once (intermediate), ether twice (both intermediate), cyclopropane once (massive), and Other once (ethylene, massive).

The occurrence of 19 instances of "unexplained" hepatic necrosis in a necropsy population of 10,171 persons (with abdominal necropsy examination) exposed to anesthesia may be taken to indicate that the liver is only rarely vulnerable to an anesthetic agent. The question at issue, however, is: "Does halothane have a greater role in this respect than other agents?" In this small group halothane appeared to be a more common offender.

It is obviously possible that anesthetic-induced hepatic disorder also occurred among those cases ascribed to definable causes in the "explained" category. And it is equally plausible to argue that an undetected factor, other than an anesthetic, may have prevailed in the "unexplained" group. If one deals only with the results of the methodology used, whatever its crudities, one may conclude that, among the 10,171 necropsied persons subjected to anesthesia (and among the 197 patients with massive and intermediate hepatic necrosis), there were 19 in whom the hepatic process might reasonably have been attributed in some way to the anesthetic used. Of these, 14 patients had received halothane and five had received other anesthetics.

Specific Lesion Caused by Halothane

Once the category of "unexplained" hepatic necrosis had been established, an effort was made to distinguish a histologic pattern that might reflect the specific effects of halothane and aid in the distinction of the lesion from that appearing after the administration of other agents. As indicated above, members of the Pathology Panel were unable to find a common meeting ground to derive such a conclusion.

In a further effort, sections from the 19 cases were intermixed with those from 19 "explained" cases selected at random and examined by one member of the Panel* without recourse to clinical information until the analyses were completed. Of the 19 "explained" cases, 17 fell among the group ascribed to "shock, anoxia, or sepsis"; six of the 19 "unexplained" cases exhibited such lesions.

As in the original survey, many variations appeared related to the duration of the lesion. Thus, a necrotic zone might exhibit cytoplasmic coagulation (Fig. 18) and disintegration in some sections, and "fallout" in others (Fig. 11); the one would reflect a recent lesion, and the other, one of longer standing. This was also the case with intralobular inflammatory reaction; cases of recent origin exhibited little or no exudate; those of longer duration exhibited a neutrophil reaction reaching from the margin of necrosis and ultimately intermingling with the nonviable cells. Cases characterized by "fallout" exhibited little neutrophil reaction; here, macrophages prevailed, but with varied prominence. Except in one instance (case 98, Fig. 10), parenchymal fat was purely adventitious. Regeneration was evidenced by irregular swelling of residual liver cells, multinuclearity, and, rarely, mitoses (Fig. 12). These changes were paralleled by periportal ductular proliferation, which, however, was not striking. Such bile stasis (cast formation) as occurred was limited to these ductules and was rarely marked.

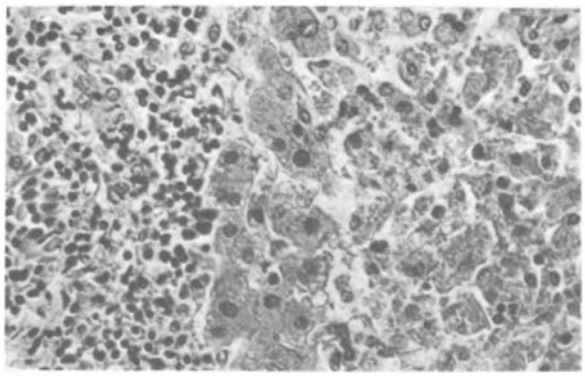

Figure 18.--Massive necrosis (Case 36). A residual periportal island of viable parenchyma borders the necrotic lobules in which coagulated and disintegrating cells have not yet lost individuality. Contrast with Fig. 10. Hematoxylin and eosin. ×200 (See Fig. 8)

*E. A. Gall.

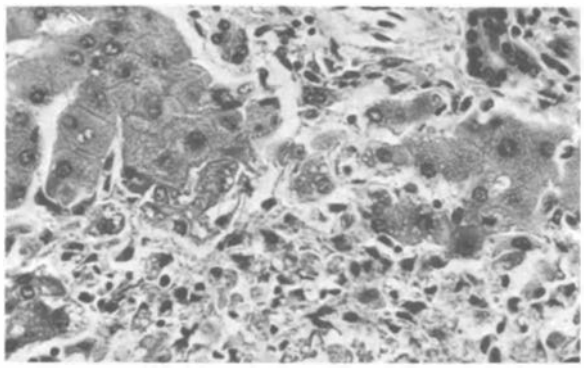

Figure 19.--Massive necrosis with portal area exudate (Case 44). Coagulation necrosis has destroyed all but two- or three-cell-layered periportal lamina. The portal area itself is heavily infiltrated with lymphocytes; this was a feature of all portal areas in this liver. Hematoxylin and eosin. × 200 (See Fig. 13.)

In 15 cases (13 "unexplained" and two "explained"), the portal areas exhibited enlargement, edema, and inflammatory (mononuclear) reaction of rather marked degree. In 12, the distribution of this process was universal, affecting all portal areas (Figs. 13 and 19) (8). Of the "unexplained" cases, 11 were patients who had received halothane; one was given nitrous oxide-barbiturate and one, cyclopropane. In neither of the two cases of "explained" necrosis was halothane involved.

Although there was no unique or consistent lesion reflecting the effects of halothane administration, the feature of severe and universal portal area inflammation occurred with significantly greater frequency in the small group of "unexplained" cases in which halothane was the agent used. None of the other histologic changes (distribution, type or degree of necrosis, type of intralobular exudate, etc.) appeared to have any pertinence. It is noteworthy that neither canalicular bile stasis nor a prevalence of eosinophils appeared in any of the cases. The pattern of portal area inflammation, however, is not unfamiliar to the pathologist; it has also been observed in cases of fatal hepatic disease of other causation, notably in fatal viral hepatitis (18) and in some drug intoxications (7,9,17,18).

SUMMARY

A pathologic survey concerned with the incidence and nature of hepatic necrosis was carried out in 10,171 necropsy cases. These were all the cases in which there had been complete necropsy, including examination of the abdomen. Variations in diagnostic criteria and nomenclature in the different participating hospitals, in methods of classification, and in screening techniques interfered with proper case selection. Despite this, it is believed that all examples of massive hepatic necrosis and almost all those with intermediate necrosis among cases necropsied were brought to light.

A scrutiny of necropsy diagnoses by varied means led to the accumulation of 972 cases of possible hepatic necrosis; microscopic sections of 946 of the livers were procured for review.

A panel of six pathologists, experienced in hepatic disorders, reviewed the sections obtained independently and with no knowledge of the clinical history or anesthetic used. Hepatic necrosis of various degrees was found in 222 cases: 82 massive, 115 intermediate, and 25 minor and deemed negligible.

The Pathology Panel next attempted to assign a cause for the hepatic necrosis, combining a knowledge of the clinical data (except the anesthetic used) and the histologic pattern of the liver. Except for recognition of the effects of anoxia, shock, or sepsis, the Panel was not able to determine an etiologic basis for the lesions with any degree of uniformity or consistency.

The histologic appearances of sections from 19 cases with necrosis, considered by a multispecialty committee to be "unexplained" by factors detectable in the clinical record, were critically studied and compared with 19 cases in which the hepatic necrosis was deemed to be the result of overt factors. No consistent histologic pattern could be attributed to halothane. It appeared, however, that cases associated with halothane exhibited a lesion simulating that encountered in fatal viral and some drug-induced forms of hepatitis more often than cases associated with other anesthetics.

In respect to the apparent relationship, three questions may be posed:

(1) Had the patient harbored a clinically inapparent viral hepatitis that had progressed by spontaneous exacerbation to a fatal outcome?

(2) Had an occult and seemingly innocuous viral hepatitis been provoked into violent progression under the stress of a complicating disease, the surgical procedure required for its correction, or the anesthetic used?

(3) Had the hepatic disorder been induced de novo by the anesthetic, either as a direct toxic effect or by reason of idiosyncrasy?

Unfortunately, the evidence gathered does not permit unequivocal affirmation of any of the assumptions implicit in these questions. One may suspect that in a rare person exposed to halothane a special sensitization constitutes a triggering mechanism, but there is no indication that this was regularly the case or that one or the other mechanisms may not have existed equally as well.

CONCLUSION

The incidence of massive hepatic necrosis in a large postoperative necropsy population was exceedingly low. Moreover, in the bulk of such cases the hepatic lesions were readily attributable to such factors as shock, infection, anoxia, pre-existing disease, and even extensive surgical manipulation. Only rarely did the anesthetic appear to be involved: in 19 cases of massive

and intermediate necrosis among the 10,171 necropsied cases investigated. Of these, 14 cases involved halothane, and five did not. No clear-cut or universally acceptable histologic lesion was regularly found in the cases attributed to halothane.

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CHAPTER III-3. ANALYSIS OF MASSIVE HEPATIC NECROSIS DATA

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The National Halothane Study was initiated to determine whether the few cases of massive hepatic necrosis reported to have occurred after halothane anesthesia might reflect a much higher incidence of unreported cases. The study of hepatic necrosis, described in the preceding two chapters, failed to uncover the large number of cases feared. On the contrary, the incidence of massive hepatic necrosis after halothane was very small, and differed little if at all from that after the other anesthetic practices. The very scarcity of observed cases makes it difficult to draw conclusions about other specific, more-probing questions. Lack of necropsy material for some of the deaths, possible "volunteer bias" in the selection of the participating institutions, and prior publication of about half the so-called "unexplained" cases add to the difficulty of interpreting the hepatic necrosis data.

THE OVER-ALL INCIDENCE OF MASSIVE HEPATIC NECROSIS

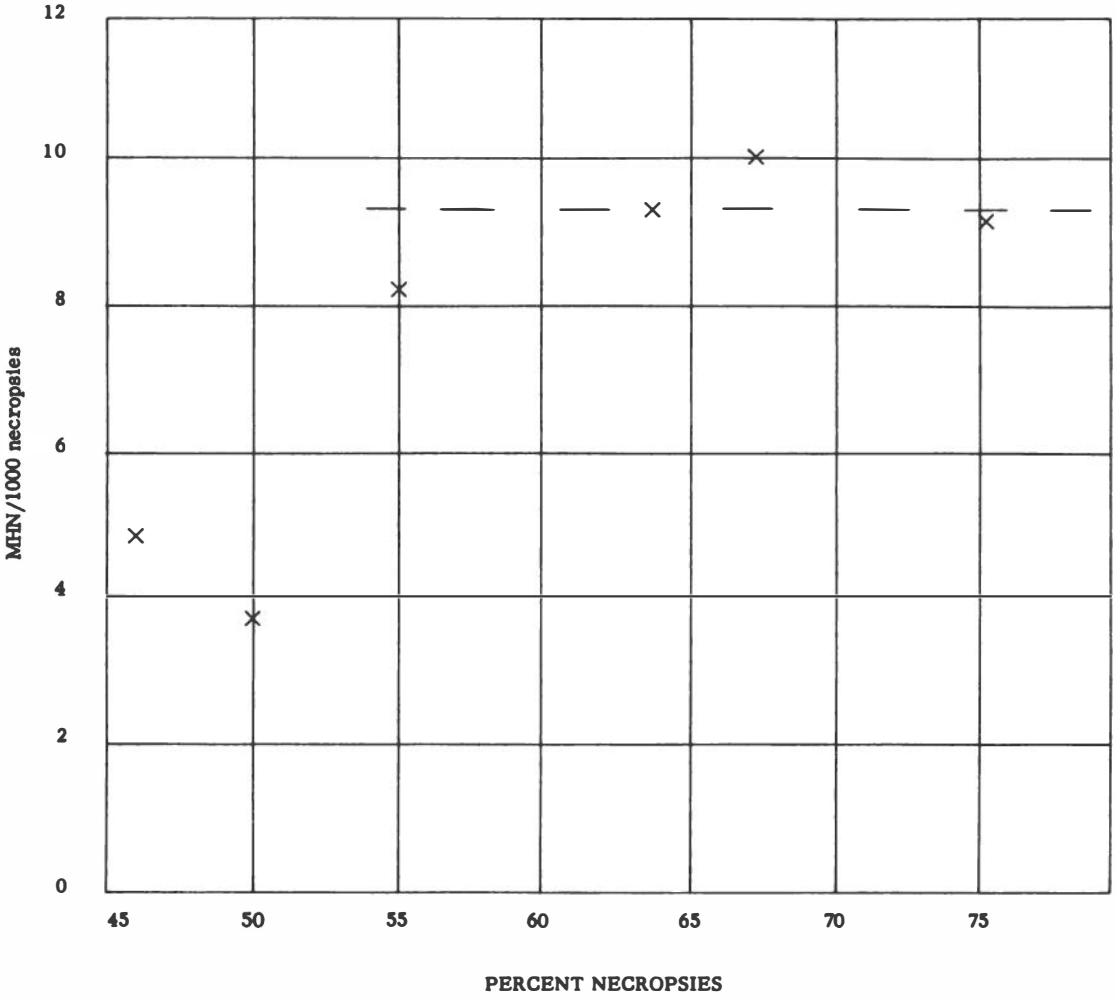
During the 4 years reviewed, 856,515 administrations of general anesthesia were followed within 6 weeks by 16,840 deaths. Of these deaths, 10,171 had necropsies that included examination of the abdominal cavity. Among these necropsied deaths, 82 instances of massive hepatic necrosis were identified by the procedures described in Chapter III-1. To estimate the over-all incidence of massive hepatic necrosis, we must consider the nonnecropsied cases and we must also consider the possibility that some cases among those necropsied could have escaped detection.

The possibility that massive hepatic necrosis could be overlooked at necropsy was judged to be slight by the members of the Pathology Panel. Some support for this opinion was provided by a site-visit review of six institutions conducted by William H. Forrest, Jr., and John P. Bunker. Review of the complete necropsy reports of all cases at those institutions uncovered no new cases that seemed likely to involve massive hepatic necrosis. Although this limited review does not preclude the loss of a few cases by clerical or diagnostic error (as discussed in greater length in Chapter III-1), the loss of cases of massive hepatic necrosis in the necropsied deaths can probably be regarded as of relatively minor importance.

The loss of cases of massive hepatic necrosis in deaths not examined by necropsy is clearly of greater importance, although it is difficult to estimate how great. On first thought, it seemed likely that when a patient died in clinical hepatic failure every effort would be made to obtain necropsy, because of the widespread interest in disorders of the liver. However, in a review of the clinical summaries of the 6669 deaths in which there was no necropsy (or in which necropsy did not include examination of the abdomen), hepatic failure was judged to have been a major contributing cause of death in 241. Thus, a considerable number of potential cases of massive hepatic necrosis were lost by failure to obtain a necropsy. On the other hand, the diagnosis of hepatic failure was made in only about one-third of the 82 necropsy-confirmed cases of massive hepatic necrosis. Thus, suspicion of hepatic injury cannot be relied on either to identify the majority of possible cases or to ensure necropsy.

Some appraisal of the incidence of massive hepatic necrosis in the nonnecropsied deaths can be obtained by comparing the rate of massive hepatic necrosis per necropsy in institutions with high necropsy rates with that observed in institutions with low necropsy rates. To do this, the institutions were first ranked by necropsy rates and separated into seven groups, each group having approximately the same number of deaths. In Fig. 1, the number of cases of massive hepatic necrosis per 1000 necropsies is plotted against the necropsy rate for each of these homogeneous groups. This graph suggests that the number of massive hepatic necrosis cases per 1000 necropsies is nearly constant at nine for those groups of institutions with necropsy rates of 55 percent or more. If it is assumed that the rate of massive hepatic necrosis per death is approximately the same for all institutions (see below), it is apparent that institutions with necropsy rates below 55 percent are deficient in cases of necrosis. And Fig. 1 suggests that, if all deaths had been necropsied, there might have been about nine cases of massive hepatic necrosis per 1000 deaths. At this rate, the study would have produced about 153 (9×17) such cases, almost twice as many as the 82 actually identified at necropsy.

Figure 1.--The relationship between the number of massive hepatic necrosis cases per 1000 necropsies and the percent of deaths necropsied for seven groups of institutions. Institutions with similar necropsy rates were pooled in groups of about 2000 deaths.



IMPLICATIONS OF THE MISSING CASES AND THE POSSIBILITY OF NECROPSY BIAS

The conclusion that a substantial portion of the massive hepatic necrosis cases was not identified is disturbing, because some of the factors determining whether a case was necropsied are related to those being studied. For example, if hepatic failure and death occurred in a patient who had received halothane, already under some suspicion during the years studied, necropsy might have been more likely to be performed. The limited death-certificate information available on the nonnecropsied cases is consistent with such a hypothesis: of the 241 nonnecropsied cases with clinical evidence of hepatic failure, 50 (21 percent) received halothane; halothane accounts for 30 percent of all general anesthetics in the Study, 28 percent of all deaths, and 29 percent of necropsied deaths. But because death-certificate information is notoriously unreliable, these data can be taken only as indicating the possibility of necropsy bias.

INCIDENCE OF MASSIVE HEPATIC NECROSIS BY ANESTHETIC PRACTICE

We now turn to the analysis of the 82 cases of massive hepatic necrosis actually observed in the Study, keeping in mind the reservations implied by the preceding discussion.

Insofar as the occurrence of massive hepatic necrosis is related to the same factors that determine the patient's prognosis, such as the type of operation or the patient's age, the rate of massive hepatic necrosis per death (or per necropsy) should remain fairly constant. Thus, we would predict the same number of cases of massive hepatic necrosis per 1000 deaths for patients undergoing low-risk operations as for patients undergoing high-risk operations. At the same time, the rate per anesthetic administration would vary

considerably, compared with the rate per death. This is well illustrated by the right-hand column of Table 1; although the rate per 10,000 estimated administrations (EA) varies from 0.08 to 5.18, among the three groups of operations, the rate per 1000 deaths varies only from 3.55 to 5.03. We choose to study the rate of hepatic necrosis per death because it provides better control for such factors as physical status and severity of operation than does rate per administration. This choice is quite consistent with the finding that, in 73 (89 percent) of these 82 cases, the occurrence of massive hepatic necrosis could be attributed to factors not directly related to the anesthetic agent, such as shock or overwhelming infection. Examination of Table 1 shows that, except for the excess of massive hepatic necrosis cases after cyclopropane in the middle-risk group of operations, there is little difference between the number of cases observed and the number expected under the hypothesis of no anesthetic differences.

CASES POSSIBLY RELATED TO THE ANESTHETIC USED

Although the incidence of massive hepatic necrosis after halothane was virtually the same as that for the over-all Study (Table 1), this does not preclude the direct association of some of these cases with the use of halothane. The efforts to identify a medical syndrome and a pathologic lesion associated with the use of halothane are discussed in Chapters III-2 and III-4. In this chapter we consider the possible association of halothane and hepatic necrosis more from a statistical point of view.

Table 2 presents the observed and expected incidences of massive hepatic necrosis categorized by previous exposure to halothane and by the possibility of explanation on the basis of clinical history. The categories of "explained" and "unexplained" were assigned by four physician members of the Subcommittee independently, and the cases so classified are those on which a majority agreed. (The details of that review are given in Chapter III-1.) The numbers of expected cases in Table 2 are computed from the necropsies. By using the number of necropsies as the base, rather than the number of anesthetic administrations, we partially correct both for the possibility that one agent was used by preference in more hazardous cases and for variations in the necropsy rates.

TABLE 1.--OBSERVED AND EXPECTED OCCURRENCE OF MASSIVE HEPATIC NECROSIS FOLLOWING HIGH-, MIDDLE-, AND LOW-DEATH-RATE OPERATIONS

Operation Group		Hal	N-B	Cyclo	Ether	Other	Total
Low-death-rate operations	Necrosis observed	2	0	1	0	0	3
	Necrosis expected*	0.8	0.7	0.6	0.2	0.6	2.9
	Number of deaths	234	209	175	63	163	844
	EA (in thousands)	86.7	105.3	67.5	50.1	57.4	367.0
	Rates/1000 deaths	8.55	0.0	5.71	0.0	0.0	3.55
	Rates/10,000 EA	0.23	0.0	0.15	0.0	0.0	0.08
Middle-death-rate operations	Necrosis observed	13	6	17	4	7	47
	Necrosis expected*	12.5	8.6	11.7	4.1	10.1	47.0
	Number of deaths	2562	1757	2397	837	2073	9626
	EA (in thousands)	146.2	101.3	68.1	44.3	67.5	427.4
	Rates/1000 deaths	5.07	3.41	7.09	4.78	3.38	4.88
	Rates/10,000 EA	0.89	0.59	2.50	0.90	1.04	1.10
High-death-rate operations	Necrosis observed	11	9	7	1	4	32
	Necrosis expected*	10.4	6.7	6.4	2.5	6.1	32.1
	Number of deaths	2066	1323	1270	492	1205	6356
	EA (in thousands)	21.8	11.6	11.7	7.6	9.1	61.7
	Rates/1000 deaths	5.32	6.80	5.51	2.03	3.32	5.03
	Rates/10,000 EA	5.05	7.78	5.99	1.31	4.40	5.18
Totals	Necrosis observed	26	15	25	5	11	82
	Necrosis expected**	23.7	16.0	18.7	6.8	16.8	82.0
	Number of deaths	4863	3292	3845	1396	3444	16840
	EA (in thousands)	254.9	218.2	147.4	102.0	134.0	856.5
	Rates/1000 deaths	5.35	4.56	6.50	3.58	3.19	4.87
	Rates 10,000 EA	1.02	0.69	1.70	0.49	0.82	0.96

*Necrosis expected (H) $= \frac{\text{total necrosis} \times \text{deaths (H)}}{\text{total deaths}}$

$= \frac{3 \times 234}{844} = 0.8$

**Total necrosis expected is the sum of those expected in the three categories of operations.

The expected numbers present a remarkably good fit with the observed numbers in categories where more than one operation was performed. In the group of patients with only one operation, halothane has six fewer cases of "explained" massive hepatic necrosis than expected (these are only partially balanced by the three "unexplained" cases in this group). The fact that the high rate of "explained" massive hepatic necrosis after cyclopropane in the single-operation group (the observed number is almost twice the expected) does not appear in the group with multiple operations is something of an enigma. If the over-all high rate of necrosis is due to the selective use of cyclopropane for patients with poor preoperative physical status and increased likelihood of shock, why does this not hold for the multiple operations as well?

If the two parts of Table 2 dealing with multiple operations are combined and the operations are classified with respect only to whether they involved halothane, the result is Table 3. Here we see that the few operations that involve two or more exposures to halothane have a higher rate of massive hepatic necrosis than the other groups. Because these comparisons are based on so few cases of massive hepatic necrosis, they are particularly sensitive to sources of bias. Unfortunately, the use of existing data, rather than those generated by a randomized study, makes it impossible to prevent such sources from operating. The small amount of information makes it impossible to control for such factors in the analysis. For example, we cannot control for the possibility that institutions vary not only in their death rates and in their use of the different agents, but also in the types of cases that they tend to examine by necropsy; nor could we assign cases to be examined by necropsy at random to avoid such a source of bias.

THE "UNEXPLAINED" CASES

Seven of the nine patients with "unexplained" massive hepatic necrosis had received halothane during the final operative procedure. Five of the seven died after clinically evident hepatic failure; this was in contrast with the patients whose massive necrosis was considered explained by prolonged shock or overwhelming sepsis, and in most of whom hepatic failure was not suspected clinically. The microscopic pattern of hepatic injury in six of the seven "unexplained" halothane cases resembled that observed in viral or some drug-induced forms of hepatitis, again in contrast with the microscopic pattern of the "explained" group, which was in almost every case consistent with the effects of shock.

It is not possible to say whether the very few cases of "unexplained" hepatic necrosis were caused by halothane or were due to other factors. For example, they may have been the result of pre-existing or unrecognized viral hepatitis, which they resembled both clinically and pathologically. The principal considerations that 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 hepatic failure might have been more likely to undergo necropsy if halothane had been administered, as discussed above. 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 over-all necropsy rates, which were almost identical in the five anesthetic groups. The period of study, 1959-1962, was explicitly chosen to antedate the widespread concern that began early in 1963 and to minimize necropsy bias. Massive hepatic necrosis after halothane had been reported as early as 1958 (1,2), however, and some suspicion must have been entertained during the period of the Study.

Confidence in comparisons among agents in this very small group of patients is further weakened by the fact that approximately 40 percent of the deaths were not necropsied or were necropsied without examination of the abdomen. This 40-percent loss in necropsy represents such a high rate of nonresponse that confidence limits on rates computed from the completed necropsies would be so broad as to be useless or would be based on strong assumptions that we are not in a position to verify.

Reports of four of the seven "unexplained" massive hepatic necroses after halothane had been published, and another 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 those cases. Thus, the inclusion of those cases in any comparison of hepatic necrosis rates for different anesthetics could lead to a "volunteer" bias in the over-all estimate of the rate of massive hepatic necrosis after halothane. To illustrate the possible effect: If an event has a low rate of occurrence, perhaps 0.2 per institution per observation period, and if we were to pick only institutions in which at least one event had occurred, then the method of selection would yield an average of 1.2 (or a bias of about five cases in our Study, inasmuch as five institutions would be affected). Thus, in the present Study, the bias would be more than enough to account for the apparent small excess of "unexplained" halothane cases. Because of this source of bias, we have listed the literature cases separately in Tables 2 and 3.

As a final point in the consideration of the "unexplained" cases and the apparent excess of

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TABLE 2.--"EXPLAINED" AND "UNEXPLAINED" MASSIVE HEPATIC NECROSIS BY EXPOSURE TO HALOTHANE AND CYCLOPROPANE

Anesthetic		Number of necropsies*	"Explained" MHN		"Unexplained" MHN		Total MHN
			Obs.	Exp.	New	Literature	
SINGLE OPERATIONS:							
H		2595	10	15.7	1	2	13
C		1890	20	11.4	1	0	21
Neither		4272	23	25.9	0	0	23
TWO OPERATIONS:							
Prev.**	Last						
H	H	262	4	1.8	2	1	7
H	C	69	0	0.5	0	0	0
H	Neither***	143	0	1.0	0	0	0
noH	H	323	2	2.2	0	0	2
noH	C	414	3	2.8	0	0	3
noH	Neither	826	5	5.7	1	0	6
THREE OR MORE OPERATIONS:							
Prev.**	Last						
H	H	43	1	0.5	0	1	2
H	C	6	0	0.1	0	0	0
H	Neither***	17	0	0.2	0	0	0
Mix	H	47	1	0.6	0	0	1
Mix	C	25	0	0.3	0	0	0
Mix	Neither***	52	0	0.6	0	0	0
noH	H	41	1	0.5	0	0	1
noH	C	90	1	1.1	0	0	1
noH	Neither***	174	2	2.1	0	0	2

*The number of necropsies includes 1118 partial necropsies in which the abdominal cavity was not examined.

**The only datum recorded for previous operation was whether halothane was used.

***Because of the small number of cases, the anesthetic practices other than halothane and cyclopropane are pooled into one group called "neither."

TABLE 3.--SUMMARY OF NECROPSIES AFTER MULTIPLE EXPOSURES

Previous operation	Last operation	Number of necropsies	"Explained" MHN		"Unexplained" MHN		Total MHN
			Obs.	Exp.	New	Literature	
H	H	352	6	3.0	2	2	10
H	noH	312	0	2.7	0	0	0
noH	H	364	3	2.7	0	0	3
noH	noH	1504	11	11.7	1	0	12

halothane cases in this special group, it must be appreciated that separating out the "unexplained" cases leaves fewer "explained" halothane cases than expected. We have no explanation for this deficit.

The data on intermediate hepatic necrosis appear to be similar to the massive necrosis data. There was an excess of halothane cases in total as well as in "unexplained" intermediate necrosis. But for this group of patients, submission bias almost certainly occurred. Cases involving lesser degrees of necrosis were submitted only as possible massive necrosis, and there was evidence that a doubtful case was more likely to be submitted if halothane had been the anesthetic agent. An example of this bias is provided by the distribution of anesthetic agents among the cases of missing data. Of the 41 pieces

TABLE 4.--RATES OF MASSIVE HEPATIC NECROSIS PER 100 DEATHS BY INSTITUTION AND ANESTHETIC

The first column under each anesthetic agent gives the rate per 100 deaths, when this is not zero; the second column, the number of deaths observed.

Institution	H		N-B		C		E		O		MHN per 100 deaths	MHN's/ deaths
1	1.1	189		55		7		5		38	0.7	2/294
2		226		94	1.1	177		22		95	0.3	2/614
3		25		106		20		1		49	-	0/201
4		105		98	1.3	223		94		197	0.4	3/717
5		333		267	0.9	346		55		196	0.2	3/1197
6		90		103		23		56	1.7	60	0.4	1/332
7		152		45		98		58		189	-	0/542
8	0.4	671	0.9	115	2.0	51	0.3	299	1.9	212	0.6	8/1348
9	0.8	261	0.4	256	0.8	121		235		103	0.4	4/976
10	0.8	228	1.3	152	1.0	295	2.4	42		82	0.9	7/799
11		128	2.8	71	1.2	84		122	0.7	150	0.7	4/555
12	0.6	178		30	1.2	173		7		116	0.6	3/504
13		71		12		98		2		63	-	0/246
14		28		11		56		6		40	-	0/141
15		64		129	1.1	190	1.6	61		142	0.5	3/586
16		67	0.4	253		81		3		115	0.2	1/519
17		52		8		19		18	2.2	89	1.1	2/186
18		73		75	0.8	124		10		45	0.3	1/327
19	0.4	228		80		97		2		79	0.2	1/486
20	2.3	43		41	0.8	245	0.8	131	0.4	267	0.7	5/727
21	0.8	248	1.6	185	0.5	185		20	0.9	177	0.9	7/815
22	1.6	243	2.2	92		138		8		133	1.0	6/614
23		18		40		19		0		6	-	0/83
24	2.0	147	0.6	514	0.4	229	3.7	27	1.7	118	1.0	10/1035
25		126		50		166		23	0.5	213	0.2	1/578
26		125		131		78		10		48	-	0/392
27		98		30		113		6		49	-	0/296
28		10		5		0		2		2	-	0/19
29	2.2	89		15		35		2		30	1.3	2/171
30	2.3	130		47	7.7	26		0		20	2.2	5/223
31		59		23		79		1		18	-	0/180
32		137		14		68		0		57	-	0/276
33	0.5	210		140		106		63		162	0.1	1/681
34		11		5		75		5		84	-	0/180
TOTAL DEATHS		4863		3292		3845		1396		3444		

of missing data (see Chapter II-2), only two were from patients who had received halothane. We conclude that a greater effort was made to provide data for halothane cases than for others.

RATES OF MASSIVE HEPATIC NECROSIS BY INSTITUTION

Differences in the standardized death rates among institutions are discussed in Part IV. It is of interest here that such differences do not seem to manifest themselves in the massive hepatic necrosis rates. Table 4 shows the rate of massive hepatic necrosis per 100 deaths by institution and by anesthetic. Again we compute the rate per 100 deaths in order to control for the patient population being treated in the various cells. The table is remarkable for the uniformity of the rates, considering the wide variety of institutions in the Study. The highest rate in a cell with at least 150 deaths is 1.9 per 100 deaths, and it occurs in an institution with 212 deaths in the cell associated with the anesthetic class "Other." When the number of cells with 150 or more deaths is considered, this occurrence is not at all extreme; in fact, it is not even remarkable, except perhaps for being small.

When we look at institution totals, instead of single cells, we observe that institution 30 has a rather high number of massive hepatic necroses for its deaths, 2.2 per 100 deaths. In studying the variability for institutions, we found the rates to be about two standard deviations larger than would be expected if all institutions were alike. Institution 30 made the whole difference, with five massive hepatic necroses, compared with 1.1 expected. No other institution had a notable rate. Thus, institutions do not separate into two good-sized clumps, for example. Whether there is any special reason for institution 30's record cannot be known without breaking the code. At any rate, except for this institution, further institutional studies are not warranted by these data.

CONCLUSIONS

It is impossible to give a precise figure for the incidence of massive hepatic necrosis in the Study, because only 60 percent of the deaths were examined by complete necropsy. An over-all rate of nine per 1000 deaths is suggested by the data, however. This is equivalent to slightly less than one per 5000 operations and includes an allowance for the cases that were not necropsied. The over-all rates were about the same for the different anesthetic practices, with the possible exception of cyclopropane, which was slightly higher than the others.

When cases of massive hepatic necrosis that could not be explained on the basis of a clinical history of sepsis or shock were picked out, it was found that seven of the nine such cases involved halothane. When the cases that could be so explained were examined, cyclopropane was found to be associated with almost twice as many as would be expected on the hypothesis of no differences among the agents. Cases involving multiple operations were also found to have a higher incidence of massive hepatic necrosis and, of these, cases involving multiple exposure to halothane were found to have the highest incidence.

These results must be interpreted with caution for two reasons. First, the lack of randomization and the fact that only 60 percent of the deaths were necropsied completely are certain to introduce biases. Second, there are so few actual cases that the analysis could neither estimate these biases nor hope to correct for them.

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CHAPTER III-4. THE CLINICAL SYNDROMES ASSOCIATED WITH POSTOPERATIVE HEPATIC NECROSIS

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Eighty-two cases of massive hepatic necrosis were identified and confirmed by members of the Pathology Panel during the Study. Complete hospital records were available for 80 of the 82 cases, thus affording an unusual opportunity to examine the clinical manifestations of postoperative hepatic necrosis. This chapter presents the findings of that review.

METHOD

The hospital records of 80 of the 82 cases were reviewed and categorized on the basis of clinical features. Particular attention was paid to the presence of shock and heart failure, and their relationship to any clinical evidence of hepatic disease that developed during a patient's illness. Cases were selected solely on the basis of postmortem hepatic histology, so that it was possible that a patient might have histologic massive hepatic necrosis without having displayed any symptoms of hepatic disease during life; in fact, that proved to be the most common situation.

The pertinent features abstracted from the hospital records are listed in Table 1. In addition, a history of hepatic disease was noted, as was any comment regarding epidemiologic factors associated with toxic or viral hepatitis (e.g., occupational exposure to jaundiced persons, medications taken before admission, and alcoholism). Blood and plasma transfusions were noted. The operative notes and anesthetic records were reviewed, with particular attention to all the anesthetics used, to the duration of operation, to the occurrence of hypotension during operation, and, where available, to the operative findings in the right upper quadrant of the abdomen. Shock was defined as a fall of 25 percent from admission levels in either systolic or diastolic pressure lasting 30 min or more, by the development of acute renal failure, or by the need for vasopressor drugs. Congestive failure was indicated by dyspnea and an enlarged heart, increased venous pressure, and the need for digitalis during hospitalization. Finally, the results of the necropsy were recorded.

TABLE 1.--INFORMATION RECORDED FROM THE HOSPITAL RECORDS OF PATIENTS WITH MASSIVE HEPATIC NECROSIS

Signs and symptoms suggestive of hepatic disease:
Gastrointestinal symptoms
Jaundice
Ascites
Palpable liver
Confusion or coma (including results of lumbar puncture)
Laboratory findings suggestive of hepatic disease (actual values recorded):
Bilirubin
Alkaline phosphatase
Transaminase (SGOT)
Serum albumin and globulin
Prothrombin time
Measurements of cardiovascular and renal status:
Pulse
Blood pressure
Venous pressure
Serum urea nitrogen
Serum creatinine
Urinary output
Evidence of bleeding:
Presence and site of bleeding
Hematocrit or hemoglobin
Stool guaiac
Evidence of sepsis:
Temperature
White-blood-cell count
Cultures for bacteria

RESULTS

Two broad categories of clinical disturbance emerged: (1) cardiovascular, in which hepatic disease was probably the result of shock or congestive failure; and (2) hepatitis, in which hepatic disease could not be accounted for on a cardiovascular basis. In general, patients in the cardiovascular category experienced an episode of hypotension or acute congestive heart failure before any clinical manifestation of hepatic disease,

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TABLE 2.--ILLNESS ASSOCIATED WITH HEPATIC NECROSIS IN PATIENTS IN THE CARDIOVASCULAR CATEGORY

Heart disease (25):		
Congenital heart disease	12	
Rheumatic heart disease	7	
Acute myocardial infarction (diagnosed at necropsy)	3	(1 without hypotension)
Malignancy involving pericardium	2	(1 without hypotension)
Myocarditis	1	(without hypotension)
Diseases of blood vessels (10):		
Aneurysm of aorta	5	
Aneurysm of internal carotid artery	1	
Thrombosis abdominal aorta	1	(without hypotension)
Thrombosis hepatic vasculature (1 associated with malignancy)	3	(1 without hypotension)
Bleeding (9):		
Gastrointestinal (2 associated with malignancy)	7	
Malignancy with bleeding tendency	2	
Sepsis (14):		
Peritonitis (2 associated with malignancy)	8	
Malignancy with abscess	3	(1 without hypotension)
Miscellaneous	3	(1 without hypotension)
Severe trauma	3	
Other malignancies	4	

TABLE 3.--OPERATION ASSOCIATED WITH EVENT LEADING TO HEPATIC NECROSIS IN PATIENTS IN THE CARDIOVASCULAR CATEGORY

Laparotomy (25):	
Exploratory	11
Vagotomy and pyloroplasty	2
Gastrectomy	5
Colectomy	1
Enteroenterostomy	1
Gastroenterostomy and choledochojejunostomy	1
Whipple procedure	1
Portacaval shunt	1
Cholecystectomy	2
Cardiac surgery on bypass	19
Repair of aneurysm	5
Miscellaneous (16):	
Clip aneurysm of internal carotid artery	1
Removal of celestin tube	1
Exploration right common iliac artery	1
Aortofemoral graft	1
Inferior vena cava ligation	1
Saddle embolectomy aorta	1
Sympathectomy and pericardial poudrage	1
Thoracotomy for hemostasis	1
Above-knee amputation	1
Pneumonectomy	1
Operation not directly associated with event leading to hepatic necrosis (5 deaths from sepsis and 1 from cerebrovascular thrombosis): cases 44, 650, 675, 680, 689, and 691	6

whereas patients in the hepatitis category displayed signs and symptoms of hepatic disease without antecedent cardiovascular difficulties.

Cardiovascular Category

Sixty-five of the 80 patients were placed in the cardiovascular category. Their diagnoses and the operations most closely related to their shock or congestive failure are classified in Tables 2 and 3. It is apparent that these patients were severely ill. All but seven were hypotensive for hours or days before death; over half the hypotensive patients showed acute renal failure.

Of the seven patients who were not hypotensive, four had severe heart failure as judged by intractable dyspnea, venous pressures over 160 mm H_2O, or acute pulmonary edema; cases 675 and 717 had overtransfusion, case 645 had longstanding myocarditis, and case 807 had heart failure associated with bilateral hemothorax and pericarditis. Of the remaining three, two had thromboses of major vessels; case 223 had thrombosis in the aorta to the level of the superior mesenteric artery, and case 680 had hepatic venous thrombosis. We believe that in six patients (i.e., the four with congestive failure and the two with thromboses of major vessels) the hepatic necrosis could probably be accounted for by the vascular lesions. The seventh (case 650) is discussed below.

Clinical evidence of hepatic disease was not prominent in this group of patients. Jaundice was present in 18 patients; all but two of these patients had been hypotensive (Table 4). Jaundice was present on admission in three patients (cases

TABLE 4.--DIAGNOSES OF PATIENTS IN THE CARDIOVASCULAR CATEGORY WHO WERE JAUNDICED BEFORE DEATH

Case	Diagnosis	Onset of event, days before death		Anesthetic
		Jaundice	Shock	
1	Noted to be jaundiced on day he died	1	--	Hal
44	Jaundiced last day of life	1	3	Hal
74	History of hepatic disease	9	1	Cyclo
185	Jaundiced last day	1	2	Hal
222	Congestive failure due to aortic stenosis	5	5	N-B
234	Congestive failure; postoperative dissecting aneurysm of aorta	9	10	N-B
345	Alcoholism; hemolytic crisis 3 days before death	1	2	Hal
352	Jaundiced before death	2 hr	1	Cyclo
363	Carcinoma head of pancreas with liver metastases, biliary tract obstruction, and ascending cholangitis	On admission	-	Cyclo
605	Carcinoma stomach; biliary tract obstruction from metastasis; bleeding gastric ulcer	On admission	-	Cyclo
650	Carcinoma esophagus; lung abscess	16	-	Cyclo
658	Rheumatic mitral stenosis, mitral insufficiency, and tricuspid insufficiency*	On admission	-	Hal
666	Rheumatic mitral and aortic stenosis and aortic insufficiency*	3	4	Hal
667	Infarction of bowel with perforation of ilium, peritonitis	2	3	Hal
687	Peritonitis; thrombosis iliac artery	2	1	N-B
712	Atrial septal defect; pulmonic stenosis*	2	4	N-B
716	Jaundiced	2	1	Hal
802	Cirrhosis with bleeding varices	1	2	Cyclo

*Hepatomegaly on admission.

363, 605, and 658); one of these had rheumatoid valvulitis and an enlarged liver, and two had biliary tract obstruction from carcinoma. In 11, the jaundice developed after a prolonged hypotensive episode. In the remaining four (cases 1, 74, 650, and 687), the etiology of jaundice was not clearly related to shock or congestive failure. For example, one patient (case 687), admitted with peritonitis, developed jaundice the day before a terminal hypotensive episode. The day before jaundice appeared, he had had an iliac thrombectomy. Classification of this patient was difficult, but he was ultimately placed in the cardiovascular category because he was severely ill with a number of serious diseases before the jaundice appeared and because, after the appearance of jaundice, the course of his illness was not that of fulminant viral hepatitis (7); it is possible, however, that the jaundice resulted from viral hepatitis superimposed on his other illnesses. Case 650 was admitted with carcinoma of the esophagus, a bronchoesophageal fistula, and a mediastinal abscess. He had not shown hypotension, although jaundice appeared 16 days before death. He had been on prochlorperazine, however, and hepatic function tests were consistent with phenothiazine jaundice (SGOT, 95; alkaline phosphatase, 26; units unspecified). At necropsy, the liver showed intrahepatic cholestasis, as well as centrilobular necrosis. (These findings were not known when the patient was classified.) Classification was based on the same criteria used for case 687; the jaundice in case 650 could probably be attributed to prochlorperazine. Similar difficulties were encountered in categorizing the remaining cases.

Hepatitis Category

The remaining 15 patients (of the 80 with massive hepatic necrosis) were placed in the "hepatitis" category. Twelve developed jaundice without pre-existing shock or congestive failure. Cases 98 and 99 never developed jaundice, but were placed in the hepatitis group because they died with normal cardiovascular systems and had hepatic necrosis at necropsy (anicteric massive hepatic necrosis due to viral hepatitis has been previously reported) (7). Case 97 developed jaundice 5 days after a 4-hr bout of hypotension due to a bleeding ulcer; in the interval, however, the blood pressure was normal, urinary output was good, and the patient seemed well, so we believed that jaundice was unrelated to the preceding hypotensive episode and placed the patient in the hepatitis category.

These 15 patients were subdivided into two groups: those who had hepatitis before operation, as indicated by preoperative jaundice and increased transaminase levels (cases 81, 205, and 651); and those who developed hepatitis after operation. The three patients who had hepatitis before operation will not be considered further, except to remark that surgery is known to increase greatly the incidence of fatal hepatic failure in viral hepatitis (9).

The courses of the 12 patients who developed hepatic disease after operation are shown in Table 5. The course was similar for most of the patients. It began with fever, which developed shortly after operation, usually within 2 to 3 days. In most cases, fever was soon followed by jaundice, which deepened progressively. At that time, a tender liver could be felt in some patients. Confusion, 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 very late manifestation, usually appearing only on the last day. Except for one patient (case 723), whose course was atypical, the total duration of the illness was extremely short, the longest interval between the onset of symptoms of hepatic failure and death being 9 days. The course was similar to that described by Lucké and Mallory in patients with fulminant viral hepatitis (7).

The results of laboratory examinations of the 11 patients* (Table 6) were consistent with severe hepatocellular damage, with an elevated bilirubin and transaminase (SGOT), a moderate increase in alkaline phosphatase, and a greatly prolonged prothrombin time, which was unresponsive to the parenteral administration of vitamin K. There was a tendency for the transaminase values to fall terminally.

Two patients (cases 98 and 99) failed to develop jaundice. However, the remainder of their courses was typical of those of the group as a whole, with fever followed by central-nervous-system symptoms and rapid death. Except for terminal prothrombin times, liver-function studies were not obtained in either of these patients; the prothrombin time in each case was prolonged. Case 99 had fever on admission and central-nervous-system symptoms after brain surgery. The extent to which hepatic necrosis was responsible for his symptoms is, therefore, a matter of conjecture.

In three patients, the appearance of postoperative jaundice was delayed. In cases 255 and 328, rapid deterioration and death occurred after jaundice had disappeared. Case 723, a man with carcinoma of the prostate metastatic to the liver whose jaundice developed after a hypophysectomy, showed an unusually prolonged course. Jaundice did not develop until the 4th postoperative week, and death did not ensue until 18 days later. Nevertheless, massive hepatic necrosis was seen at necropsy, and we assume that his disease differed only in degree from the illness observed in the others.

Specific causes for postoperative necrosis of the hepatitis type were difficult to assign. The difficulty is reflected in the fact that, in seven of the 12 cases, necrosis was considered to be unexplained in the "blind" clinicopathologic review of all 82 cases of massive hepatic ne-

*No laboratory data were available on case 36.

TABLE 5.--CLINICAL FEATURES OF PATIENTS IN THE HEPATITIS CATEGORY*

Case	Operation	Onset of event, days after last operation						Remarks
		Fever	Jaundice	CNS symptoms		Bleeding	Death	
				Precoma	Coma			
36	Many dressing changes and skin grafts (total, 9 operations)	On admission	2	2	3	None	3	Temperature rose substantially (103-105 F) 4 days before onset of jaundice
51	Gastrectomy	2 days before operation	2	5	8	None	11	Plication of ulcer 2 months before death - no transfusion then
64	Cholecystectomy	--	14	17	No	None	20	
91	Excision carcinoma skin of right leg; skin graft	1	3	3	4	None	7	
97	Closure of perforated ulcer, gastric resection	2	5	8	No	None	8	
98	Tendon repair	7	No	9	9	11 (upper GI)	15	
99	Cranictomy	On admission	No	1	No	None	5	Precoma followed brain operation
100	Resection carcinoma stomach; drainage subphrenic abscess	13 days before last operation	5	5	8	None	11	Laparotomy 2 months before death - no transfusion then
122	Esophagoscopy; cholecystectomy; repair dehiscence twice	3	2	2	3	None	5	Transient fever following third operation
255	Laparotomy, biopsy	28	28	30	33	33	35	Hysterectomy 2 months before death
328	Cesarean section	33	38	38	39	40	40	
723	Hypophysectomy	1	23	29	no	None	41	Enlarged liver on admission -- probable metastatic carcinoma

*Cases 81, 205, and 651 not included because hepatitis was present before operation.

TABLE 6.--RESULTS OF LABORATORY EXAMINATIONS OF PATIENTS IN THE HEPATITIS CATEGORY

Case	Serum bilirubin, mg/100 cc		Serum alkaline phosphatase, Bessey-Lowry units		SGOT, units/ml		Prothrombin time	
	1st high value	Maximum	1st high value	Maximum	1st high value	Maximum	1st high value	Maximum
51	18 (3)*	30 (8)	4.3 (3)	4.9 (8)	720 (3)	720 (3)	39 sec (3)	44 sec (6)
64	13 (17)	19 (18)	5.9 (17)	5.9 (17)	1100 (17)	1100 (17)	10%	10%
91	11.8 (4)	18.0 (7)	10.3 (4)	10.3 (4)	740 (5)	765 (7)	40 sec (7)	40 sec (7)
97	4 (5)	10 (7)	--	--	--	--	17% (7)	--
98	--	--	--	--	--	--	10% (12)	--
99	--	--	--	--	--	--	20 sec (5)	--
100	12 (5)	21.2 (9)	--	--	262 (7)	262 (7)	12%	12%
122	8 (2)	--	10.3 (2)	--	111 (3)	--	7% (3)	--
255	25 (30)	--	1.9 (30)	--	125 (30)	--	<10% (30)	--
328	5.8 (30)	7.4 (31)	10.5 (30)	10.5 (30)	16,740 (30)	16,740 (30)	39 sec (31)	39 sec (31)
723	7.8 (-13)	--	7.5 (25)	10.1 (28)	354 (28)	--	18 sec (-13)	21 sec (26)

*Numbers in parentheses are numbers of days after final operations that the measurements were made.

TABLE 7.--TREATMENTS RECEIVED BY THE PATIENTS IN THE HEPATITIS CATEGORY THAT MAY HAVE BEEN ETIOLOGICALLY RELATED TO MASSIVE HEPATIC NECROSIS

Case	No. of transfusions 10 or more days before jaundice	Drugs reported to cause jaundice		Principal anesthetic (last operation)
		Cholestatic	Necrotic	
36	81	None	None	Hal (6)*
51	None	None	None	Hal
64	None	--	--	Other
91	1	None	Tolbutamide	Hal (2)
97	None	Promazine	None	Hal (2)
98	None	Promethazine prochlorperazine	Sulfadimethoxine	Hal
99	None	None	INH	Hal (2)
100	8	Promethazine	Sulfisoxazole	Hal (2)
122	None	Prochlorperazine	None	Hal (2)
255	None	None	None	Hal
328	5	None	None	Cyclo
723	3	Prochlorperazine	Sulfisoxazole	Hal

*Number of exposures to halothane of patients who received it more than once.

crosis. (See Chapters III-1 and III-2.) Table 7 summarizes some of the possible etiologic factors: the number of transfusions (blood and plasma) and the administration of drugs reported to be associated with jaundice, as well as the principal anesthetic agent used in the operation immediately preceding hepatic failure. Two of the three patients in whom the appearance of jaundice was delayed received transfusions 10 or more days before the onset of jaundice, whereas such transfusions were given to only three of the eight patients whose illness developed shortly after operation. Five patients received drugs of the type associated in the past with hepatic injury. (2-6,8) In four cases these were sulfonamides; the fifth was isonicotinic acid hydrazide (INH). Ten of the 12 patients whose hepatic disease was noted after operation received halothane for the final operation; of these 10, six had received halothane previously.

DISCUSSION

The two clinical categories into which we have placed the 80 cases of massive hepatic necrosis were easily distinguished. Those in the hepatitis category progressed rapidly from relatively good health through fever, jaundice, and coma, with death ensuing usually within a week of the first symptoms. Hypotension appeared only on the last day of life, and congestive heart failure was not prominent in any. In contrast, the patients in the cardiovascular category were severely ill, with prolonged shock or, less frequently, severe congestive heart failure. Half the hypotensive patients developed renal shutdown. Jaundice was an unusual manifestation, appearing in only 15 patients and then usually only terminally. In most cases, hepatic disease was not suspected during life.

Although cardiovascular disease was probably the cause of the hepatic necrosis in patients in the cardiovascular category, the etiology of the hepatic damage in patients in the hepatitis category seemed to be unrelated to shock or congestive failure. The fulminating hepatic necrosis seen in the latter patients is usually attributed to a virus or to a drug reaction.

In most of the patients in the hepatitis category, hepatic necrosis appeared within a week of operation. Three of these patients received transfusions 10 or more days before the onset of hepatic necrosis, so the disease may have been serum hepatitis. Inasmuch as the remainder had received no transfusions, their hepatic necrosis would have to be attributed either to the fortuitous appearance of infectious hepatitis during the 1st postoperative week or to a reaction to a drug given near the time of operation.

In three patients, however (cases 255, 328, and 723), as mentioned above, hepatic necrosis did not appear until several weeks after operation. All received blood or plasma at the time of operation. The interval between operation and the onset of hepatitis was probably too long for the damage to be attributed to a drug administered in connection with the operation, but is consistent with the course of posttransfusion hepatitis (1).

Medications that were given in the operative period, and that had heretofore been associated with massive hepatic necrosis, were the sulfonamides, INH, and halothane. Hepatic damage due to sulfonamides has usually been associated with other manifestations of sensitivity, such as rash, arthralgia, and eosinophilia, none of which was present in these patients; furthermore, there have been no reports of fatal hepatic damage associated with any of the particular sulfonamides given to these patients. We believe, therefore, that hepatic damage in these patients was unrelated to the sulfonamides. INH, however, has on rare occasions been associated with massive hepatic necrosis, and therefore remains a possible, although unlikely, cause of hepatic failure in case 99.

In the present series, 10 of 12 patients (83 percent) who developed postoperative massive hepatic necrosis of the hepatitis type received halothane for their final operation, whereas the over-all incidence of halothane anesthesia in the entire series of over 800,000 patients was 29.8 percent. Similarly, the percentage of patients who received multiple administrations of halothane was considerably higher among the hepatitis group (six of 15) than among the cardiovascular group (four of 65).

It is not possible, however, to conclude that halothane was responsible for the excess of patients in the hepatitis category. For example, the method of case selection introduced a bias that could have favored this hypothesis. The statistical difficulties encountered in attempting to assess the role of the anesthetic agent in such a small group of patients are discussed in detail in Chapter III-3.

SUMMARY

The National Halothane Study made available for investigation 82 postoperative instances of necropsied massive hepatic necrosis (listed in Table 8). By clinical analysis of the records of 80 of them, these patients were classified into two groups, representing different types of hepatic necrosis.

Sixty-five were classified as necrosis after vascular insufficiency due to shock, heart failure, or both. Of these, only 25 percent were jaundiced. In the icteric patients, cardiovascular insufficiency preceded jaundice in almost every instance.

Of the 15 patients whose necrosis was not explained by vascular failure, three had hepatitis (probably viral) before operation, leaving 12 with no obvious cause for their hepatic disease. These 15 progressed rapidly from relatively good health, through fever, jaundice, and coma, to death within a week of the first symptoms. All but two were jaundiced. Hypotension appeared only terminally.

TABLE 8.--CASES REVIEWED

Cardiovascular category			Hepatitis category	No chart available
1	619	685	36	647
44	620	686	51	817
55	628	687	64	
68	632	688	81	
72	636	689	91	
74	645	691	97	
93	649	692	98	
127	650	707	99	
135	653	709	100	
156	657	711	122	
185	658	712	205	
222	660	713	255	
223	664	716	328	
234	665	717	651	
338	666	718	723	
345	667	719		
352	669	724		
363	670	802		
605	673	807		
609	675	812		
616	680	824		
618	681			

Thus, postoperative hepatic necrosis is most commonly associated with vascular insult, and displays few of the clinical findings of the better known, but much less frequent, "acute yellow atrophy" of presumed drug or viral etiology.

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CHAPTER III-5. SUMMARY OF STUDY OF HEPATIC NECROSIS: CLINICAL IMPLICATIONS*

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DEGREE OF NECROSIS

The Pathology Panel 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.

The degree of necrosis was rated by each pathologist independently on a scale of 0 (none) to 4+ (total destruction of parenchyma). These ratings were averaged and the cases were separated into three categories: massive necrosis (average score, 2.6+ or above); intermediate necrosis (1.6+ to 2.5+); and minimal necrosis (1.5+ or below). Of the 222 cases, 82 were scored as massive, 115 as intermediate, and 25 as minimal necrosis. Minimal necrosis was considered to be a common and negligible occurrence in any necropsy population and these cases were thereafter disregarded.

The 82 cases of massive hepatic necrosis were collected from 10,171 necropsies, or approximately one in 125 necropsies. It was difficult to estimate the incidence of hepatic necrosis per administration of general anesthesia, because of the 6669 cases in which necropsy was not performed or the liver was not examined; but the data suggested one per 5000 administrations.

If the 115 cases of intermediate hepatic necrosis are added to the 82 cases of massive necrosis, the combined incidence is one in 2000 (or five in 10,000) administrations of general anesthesia. Any inferences drawn from the data on intermediate necrosis should be weighed with caution, however. 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.

EFFECT OF OPERATION

Operations were grouped for purposes of analysis on the basis of death rates (low, middle, and high). The low-death-rate category consisted of operations on the mouth or eye, herniorrhaphy, dilatation and curettage, hysterectomy, cystoscopy, and plastic procedures. The high-death-rate group included craniotomy, open-heart operations, exploratory laparotomy, and large bowel procedures. All other operations were arbitrarily assigned to the middle-death-rate category.

Hepatic necrosis occurred more commonly after operations associated with high death rates: there were three cases of massive necrosis after 366,992 low-death-rate operations (approximately 0.1 per 10,000), 47 after 427,355 middle-death-rate operations (1.1 per 10,000), and 32 after 61,719 high-death-rate operations (five per 10,000). Nineteen, or nearly one-fourth, of the massive necroses followed open-heart operations with cardiopulmonary bypass, although those procedures accounted for only 1 percent 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 relatively high incidences of massive hepatic necrosis.

Contrary to expectations, an increased incidence of massive hepatic necrosis did not occur after biliary tract operations. An estimated 27,677 patients underwent cholecystectomy, common-duct exploration, or both, with or without other major surgery, and massive hepatic necrosis occurred in only six of them, for a rate somewhat lower than those for most other abdominal operations. One of the six patients had received halothane, whereas halothane was administered for approximately 30 percent of

*The first five sections of this chapter (i.e., through "Pathology") were prepared by the entire Subcommittee as part of the Summary of the National Halothane Study.

the cholecystectomies and common-duct explorations. Massive hepatic necrosis occurred in an additional three patients who had undergone a biliary tract procedure previously within 6 weeks of death, and one of them had received halothane.

EFFECT OF ANESTHETIC AGENT

The highest rate of massive hepatic necrosis followed administration of cyclopropane, particularly in the middle-death-rate group. 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 percent of open-heart operations. The incidence of massive hepatic necrosis after administration of halothane was virtually the same as that after administration of nitrous oxide-barbiturate or "Other" anesthetics, slightly more than that after ether, and considerably less than that after cyclopropane.

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

There usually 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 pre-existing hepatic disease. In a few cases, however, the underlying reason for hepatic necrosis was not easily established; accordingly, four members of the Subcommittee independently reviewed 80 of the 82 cases of confirmed massive hepatic necrosis. They classified each case "explained" or "unexplained" on the basis of whether the necrosis could be assigned to a recognizable clinical factor. These ratings were made from summaries of the clinical records from each of which the identity of the anesthetic agent(s) had been deliberately omitted.

Among the 80 cases of confirmed massive hepatic necrosis, nine were considered to be "unexplained" by at least three of the four members of the Subcommittee; seven patients had received halothane for the final operation, one had received cyclopropane, and one had received ethylene ("Other"). Of the nine patients, five had undergone one or more operations previously within 6 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 and ether for the previous one.

CLINICAL SYNDROMES

"Unexplained" hepatic failure was usually characterized by fever within 2 or 3 days after operation, soon followed by jaundice, which deepened progressively, and the development of a tender, palpable liver. Confusion, 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 short, the longest interval between the onset of symptoms of hepatic failure and death being 9 days. The course was similar to that associated with fulminant viral hepatitis and to that which may follow chloroform anesthesia or poisoning by carbon tetrachloride. In contrast, the patients in whom necrosis was considered "explained" were seriously ill, usually with shock for many hours or days or, less commonly, with severe congestive heart failure. Half the patients with hypotension became anuric. Jaundice was a less common manifestation, and usually occurred only terminally. In most of these cases, hepatic injury was apparently not suspected during life.

PATHOLOGY

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 that occurred in almost all these patients before 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 on the necrotic zone.

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 thought by the majority of the members of the Pathology Panel to simulate the lesions of viral or some drug-induced forms of hepatitis. In these lesions the hepatic cellular necrosis was coagulative and sinusoidal congestion was a minor feature. Intralobular inflammation was variable and usually appeared as an intermixture of histiocytes and neutrophils among the necrotic epithelial cells. The portal areas of some cases exhibited a lymphocytic exudate. Fatty degeneration was variable, but usually negligible.

Briefly, there were nine "unexplained" cases of massive hepatic necrosis, seven after halothane. Six "unexplained" cases after halothane had a lesion simulating hepatitis, including one with histologic features that suggested superimposed shock. The lesions in the remaining three "unexplained" cases were consistent with shock; one followed administration of halothane, one followed cyclopropane, and one followed ethylene ("Other").

DISCUSSION

The National Halothane Study was designed to determine whether the use of halothane anesthesia is followed by an increased incidence of massive hepatic necrosis (when compared with other anesthetic agents). An equally important objective was to compare halothane with other general anesthetics as to total hospital mortality within 6 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 with an estimated over-all operative mortality rate of approximately 2 percent. Indeed, a slight superiority in over-all mortality for halothane could well outweigh any excess of deaths resulting from massive hepatic necrosis.

The issue is one of public health, and from this point of view halothane is as safe as or safer than other commonly used anesthetics; its fatal effects on the liver, if any, are clinically negligible. It must be stated quite clearly that the data, although limited, do provide some evidence to suggest that halothane can damage the liver, and some to suggest that it does not.

The evidence lending support to the possibility of a halothane-induced hepatic injury consists of the very small group of patients who died with clinical evidence of hepatic failure; the microscopic pattern of hepatic injury was consistent with drug-induced or viral hepatitis and most of these few patients had received halothane.

The principal reasons for doubting that halothane damages the liver--more precisely, for doubting that these few "unexplained" cases of massive hepatic necrosis after halothane were caused by halothane--are the many known and suspected biases inherent in this study of hepatic data collected in the past.

CLINICAL IMPLICATIONS

There are many questions concerning the use of halothane in the clinical practice of anesthesia whose answers would be welcomed by the practicing physician. Some of these can be provided. The over-all risk of massive hepatic necrosis after uncomplicated surgery performed with any of the commonly used anesthetic agents is so small that it can be totally disregarded as a factor in the choice of anesthetic agent under almost all circumstances. The data of the Study also allow us confidently to disclaim any special risk of fatal hepatic injury from halothane in patients undergoing biliary tract surgery, some of whom can be assumed to have suffered some degree of preoperative hepatic damage. The Study did not attempt to collect data on preoperative hepatic disease, except for the 82 cases finally identified as massive hepatic necrosis, and therefore relatively little can be said about the risk of halothane in patients known preoperatively to suffer from diseases of the liver. Other reports of the use of halothane in patients suffering from advanced hepatic disease suggest that even here there may be no special danger. With the wide variety of anesthetic techniques and agents now available, however, some may choose to avoid the use of halothane under these special circumstances.

The data collected allow us to say almost nothing about the risk of nonfatal hepatic injury. Hepatic morbidity is, of course, a consideration of no small interest and importance, and in the planning of the Study much attention was directed to the feasibility of obtaining data on nonfatal hepatic failure. It was considered essential, however, in the design of a sound protocol for the study of past data, to choose a readily identifiable criterion of hepatic injury--hence the selection of pathologically confirmed massive necrosis. The difficulty that was later encountered in achieving reliable criteria for massive hepatic necrosis strongly suggests the correctness of this decision.

Although data on nonfatal hepatic injury were not solicited, we do have information on previous operations of patients who ultimately died with massive necrosis. Approximately 80,000 (9 percent) of the patients in the Study, and 24 of the 82 patients (30 percent) who were found to have suffered massive hepatic necrosis at necropsy, underwent two or more operations in the same month or in consecutive months. If nonfatal hepatic injury were a frequent occurrence and, as has been suggested, predisposed to more severe later injury, one would expect to find evidence of hepatic injury after the earlier procedure. Careful study of these cases failed to show any such evidence. This does not, of course, prove that subclinical injury had not occurred (fewer than half the 82 patients with fatal massive hepatic necrosis gave clinical evidence of hepatic failure before death). But absence of clinical manifestations of hepatic failure after previous exposure in this highly suspect group of patients does provide some additional evidence of the infrequency of postoperative hepatic injury, fatal or nonfatal.

The possibility of a special risk of hepatic injury after repeated exposures to halothane has attracted widespread interest. Many of the published cases of massive postoperative hepatic necrosis thought to be halothane-induced did follow multiple administrations of halothane. However, in reports of patients who have received 30 or more administrations, no hepatic injury was found. In the National Halothane Study, the incidence of massive hepatic necrosis was higher after two or more general anesthetics when halothane was used at least twice, than when it was not. Many of the clinical situations which were found to be associated with higher incidences of hepatic necrosis (e.g., open-heart surgery and exploratory laparotomy) also frequently require multiple operations. Concerning the selection of anesthetic agent under these circumstances, obviously of

critical importance, we have relatively few data. With the issue unresolved, and perhaps unresolvable, how should one proceed clinically? It is clearly unwarranted to suggest that halothane anesthesia should not be repeated, for it is under the difficult circumstances of emergency reoperation that a wide choice of anesthetic agents may be most urgently needed. Furthermore, it would not be justifiable to suggest that halothane should not be used for more than one purely elective operation. When, however, a patient has suffered unexplained fever and jaundice after administration of halothane, it is the opinion of some physicians that halothane should not be used for a subsequent operation. The basis for their recommendation is the usual medical doctrine that any treatment followed by ill effects should ordinarily not be repeated. Whatever the merits of such a recommendation, it is remarkable that there was not a single patient in the National Halothane Study who was jaundiced after the administration of halothane and died after a second administration and was found at necropsy to have suffered massive or intermediate hepatic necrosis.

Although attention has been directed to patients who received halothane, the 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. Inasmuch as all but one of the 25 cases of massive necrosis that followed administration of cyclopropane 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 cyclopropane for patients in shock; but the possibility that cyclopropane damages the liver cannot be excluded.

CONCLUSIONS

Fatal postoperative massive hepatic necrosis was rare. It occurred primarily after operations associated with high death rates, and 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 after single or multiple administration could not be ruled out.

PART IV. THE STUDY OF DEATH RATES

334-553 O-69—13

Abstract of Chapter IV-1

To assess the over-all comparative safety of the several anesthetics and the magnitude of the effects of hepatic necrosis requires a study of surgical death rates. This study can provide information about the magnitude of the effects of important variables, such as sex, age, physical status, and operation, as well as information about the anesthetics. Having some firm information reduces the range of hypotheses available for explaining surgical deaths and suggests the sizes and types of studies still needed. The observed death rates supply baselines for use by various medical groups. The study has produced new methods of analysis dealing with the common problem of analyzing multidimensional contingency tables.

In a study of rare events, such as surgical deaths or, even rarer, massive hepatic necrosis, it is the number of rare events observed, rather than the number of opportunities for them to occur, that determines the stability of the averages. Consequently, very large numbers of cases are often required for analyzing rare events. As explained in the second section of this chapter, the process of carrying out unusually large studies may itself create biases and inaccuracies that can invalidate the differences observed as representative of those that are to be detected. And therefore it may frequently happen that small quantitative differences cannot be empirically established.

CHAPTER IV-1. INTRODUCTION TO THE STUDY OF DEATH RATES*

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WHAT CAN BE LEARNED?

Reports of a few postoperative deaths from hepatic necrosis in patients anesthetized with halothane, together with uneasiness about halogenated anesthetics, led to the National Halothane Study. This portion of the Study primarily compares the relative frequencies of postoperative death from all causes after the administration of the five major anesthetics (or combinations of anesthetics). Using death rate as the index emphasizes the over-all danger of the surgical procedure, including the anesthetic, rather than just the consequences to the liver.

Early in the planning phases, calculations of orders of magnitude clearly indicated that, even if halothane did lead to a higher death rate from hepatic necrosis than other anesthetics did, the fraction of deaths from this source would be numerically very small, compared with the over-all operative mortality of around 2 percent. Of this 2 percent total mortality, the deaths attributable to hepatic necrosis could account for but a small part. Indeed, if halothane were only slightly superior to other agents in over-all operative mortality, then that slight superiority could far outweigh any plausible excess of deaths due to massive hepatic necrosis. These remarks

*The first section of this chapter was written by B.W. Brown, Jr., and F. Mosteller; the second section was written by L. E. Moses, F. Mosteller, and W.M. Gentleman.

are valid whether or not experts can identify those deaths due to massive hepatic necrosis or can establish a causal connection between the use of halothane and those deaths. The issue is magnitude, rather than causation. Thus, a preliminary question was: "How do the postoperative death rates after the several anesthetics compare, first, for all patients combined, and, second, for specific classes of patients, such as those defined by type of operation, physical status (anesthetic risk), and age?"

The issue discussed briefly above, deaths from massive hepatic necrosis vs. deaths from all sources, exemplifies a common conflict of interest present in medical investigations. By identifying causes of deaths and subsequently adjusting the conditions leading to these causes, we often make scientific and medical progress. Nevertheless, appraising the consequences of a small portion of cases of a complicated medical procedure, in addition to being difficult and tenuous itself, always invites the pitfall of overlooking the total effect of the procedure on the patient population. At a ridiculous extreme, we can consider reducing the anesthetic death rate to zero by eliminating the use of anesthetics. A more realistic example would be the abandonment of penicillin because we know that a small proportion of people are allergic to it and may die from it. One important measure of the total effect of a surgical procedure is the total death rate, not just anesthetic death rate or death rate from some specific disorder, such as massive hepatic necrosis.

Naturally, a question of great medical importance, although not so primary from a public-health point of view, is whether hepatic necrosis is especially associated with halothane or with any other anesthetic. If so, what is the mechanism and how can the hepatic damage be avoided?

Fortunately, the National Halothane Study has been able to review both the problem of fatal hepatic necrosis and that of death rates. What has not been investigated by the Study, except through a survey of the literature, is the behavior of the liver and other organs in living patients before surgery and after surgery in which different anesthetics were used.

Chapter II-1 discusses the pro's and con's of studies of past data in general. Below is a description of what may be learned from a study of death rates in particular.

The Study Shows the Postoperative Death Rates That Have Been Associated With Anesthetics In the Recent Past

Historical comparison of anesthetics

If, as the establishment of a National Halothane Study might suggest, death rates among some special classes of patients have been much higher after the administration of one anesthetic, such as halothane, than after the administration of other agents, we might hope to discover that effect in the data. In the absence of such effects, we can be encouraged about the over-all safety of the anesthetic.

Effects of other variables on death rate

By examining the variation in death rates associated with other variables (e.g., hospital, type of operation, and length of operation), we can put the variation in death rates associated with anesthetics into perspective. Generally speaking, research expenditures directed toward improvement of practices in any field are more rewardingly directed toward reduction of large effects than toward small ones (unless some specific method of dealing with a small effect is in sight).

Choice of hypotheses for investigation

Above all, in any investigation of this sort, we must not underestimate the value of establishing a few facts with reasonable firmness. Before examining a large, systematically collected body of data, an investigator with a fertile mind can think of thousands of hypotheses of varying credibility. Some possible hypotheses for this Study (all false) are: (1) differences in death rates for anesthetics may be accounted for by one or two hospitals; (2) massive hepatic necrosis is entirely associated with extracorporeal circulation in cardiac operations; and (3) hospitals differ in surgical death rates only because they perform operations of different seriousness. A large body of data can often help the investigator by disposing of some hundreds of these hypotheses, thus eliminating the necessity for whole lines of investigation.

Guidance toward study size and type

By looking at the sizes and kinds of effects observed in the past, we can get an idea of the size and kind of new study required for the detection of effects. What is especially valuable is that some inquiries may be shown to be unfeasible.

Let us not overemphasize the adequacy of a historical investigation, as compared with a randomized prospective study. Retrospective studies, such as the present one, inevitably have potential biases that cannot be rooted out, satisfactorily assessed, or even identified.

To summarize, we can find out the death rates that have occurred in the past in the hospitals in the sample, and hope that the trends are similar to those of the national population of hospitals and patients. Inevitably, the retrospective information offers a better foundation for planning and policy than the guesses that must be made in its absence.

The Collection and Analysis Of a Large Body Of Data Create a Set Of Baselines With Which Various Groups Can Compare Experiences

Hospitals

Administrators of hospitals and medical investigators customarily compare the experiences of their hospitals with those of others. Only active study by qualified investigators can tell what suggestions the experience of an especially low death rate in one hospital will offer to a hospital with a higher rate. Within reason, the competitive urge for excellence can be a healthy force for achieving and maintaining high standards.

Operations

The determination of death rates that follow particular sorts of operations can similarly stimulate inquiry as to why some surgical groups achieve lower death rates for specific operations than others do. Such comparisons cannot be made in a superficial manner; consideration must be given, for example, to the composition of the patient population. Surgical teams may wish to compare their experiences on their own substantial series of operations with this larger collection of such series.

Investigations That Fall Between Correlational Analysis and Experimental Studies Help To Check Over-All Findings and Are Of Value In Themselves

Hospitals differ, sometimes radically, in their anesthetic practices. To the extent that they do, the subtle biases arising from an anesthesiologist's preferential use of agents in a particular clinical situation may be overridden. For example, one hospital in this Study used halothane in over 40 percent of its operations and cyclopropane in fewer than 0.5 percent. Another hospital used halothane in 6 percent of its operations and cyclopropane in 46 percent. Swings in usage this large surely arise from hospital or departmental policy, rather than from individual choices based on the conditions of single patients. The patient is considered, and individual choices are made, but the range of choices in the first hospital did not really include cyclopropane and in the second hospital scarcely included halothane.

Insofar as swings in usage can be attributed more to policy than to individual choices, the comparisons are freer of internal selective biases than the usual criticisms of retrospective studies would suggest. Unfortunately, we cannot make much direct use of this finding because the direct comparison of hospitals that use anesthetic A and not B with those that use B but not A would have anesthetic effects heavily confounded with hospital differences, especially if relatively few hospitals offer such pure usage and nonusage of anesthetics. Nevertheless, the indirect use of the observation of large swings as based on policy rather than on individual decision strengthens our over-all inference considerably.

To turn to the other extreme, we can make special studies based on hospitals that use two or more anesthetics extensively, thus maintaining a high level of experience with each, while controlling on hospital.

The Attempt To Analyze This Large Collection Of Data Has Developed New Methods Of Analysis

Not only in medical investigations, but also in social and engineering problems, the analysis of rates and counts associated with many background variables is a recurring and very awkward problem. In this study, we compare the anesthetics in terms of overt death rates, but the agents have been used on patients with different physical conditions. For a careful comparison, allowance should be made for such differences. And after adjustment for anesthetic risk, the patient's age must be taken into consideration, and the type of operation, etc. Obviously, the number of such allowances the investigator would like to use is not even limited by the variables he has observed.

Let us especially note the need to handle variables jointly. Variables controlled separately may not tell us the simultaneous effect of two or more variables. In some problems, effects add up simply, but in others, variables may interact so that their joint effect cannot be computed by adding up their separate effects.

Frequently, in studies of several variables, one table shows the rates associated with different ages, and another the rates associated with the sexes, as the tables of Chapter IV-2 do. Such tables adjust for variables singly, but not in combination. Less frequently, rates are computed with control on two variables, perhaps for specific age-sex classes. To go further and give rates for classes of patients described by three variables--say, age, sex, and anesthetic--the investigator would often be hard pressed for the cases needed for a reliable rate. If we use eight age classes, two for sex, and five for anesthetics (a deliberate oversimplification), we have $8 \times 2 \times 5 = 80$ classes. As further variables are added, more and more classes are created, and the most direct analysis--deaths in class divided by administrations in class--fails because a class has too few cases to lend stability to the estimate. The resulting frustration is the bane of the man who must work with counts and several variables.

It is appropriate to create new methods for handling this nearly universal problem at just this time. High-speed computers and experience with them have now developed to such a stage that we can afford to execute extensive manipulations repeatedly on large bodies of data with many control variables, whereas previously such heavy arithmetic work was impossible. The presence of the large sample from the National Halothane Study has encouraged the investigation and

development of flexible methods of adjusting for several background variables. Although this adjustment problem is not totally solved by the work in this Study, substantial advances have been made and directions for further profitable research are clearly marked.

At first, one might suppose that the needs for adjustments would be limited to nonrandomized studies and that a randomized prospective study would have no use for them because it could maintain balance. Perhaps if only a pair of numbers for the entire study were the assured goal, the randomized prospective study would not have to use adjustment; but adjustment is likely to increase precision, perhaps very substantially--an opportunity not to be missed. Some reasons are suggested below.

Pure or complete randomization does not produce either equal or conveniently proportional numbers of patients in each class; attempts at deep poststratification are doomed to failure because for several variables the number of possible strata quickly climbs beyond the thousands. Furthermore, randomization within strata during a study is rarely feasible. It is easy to ensure that sex is treated equally by randomly assigning equal numbers of women and men to each treatment. But then age will not be controlled, nor risk, nor kind of operation. To make this even clearer, consider some of the control variables used in the National Halothane Study: age, 10 categories; risk, eight categories; sex, two categories; previous operation, three categories; and operation, about 75 categories. These five variables alone produce $10 \times 8 \times 2 \times 3 \times 75 = 36{,}000$ cells. This failure of chance to equate for strata demands and rewards adjustment for the inequalities.

Briefly, the "control" that we associate with the idealized physical-science experiment is not available when we have many variables whose values we must accept, as we do with surgical patients, rather than change.

Insofar as we want rates for special groups, we need some method of estimation that borrows strength from the general pattern of the variables. Such a method is likely to be similar, at least in spirit, to some of those that were developed and applied in this Study.

At some stage in nearly every large-scale, randomized field study (a large, randomized prospective study of postoperative deaths would be no exception), the question arises whether the randomization has been executed according to plan. Inevitably, adjustments are required to see what the effects of the possible failure of the randomization might be. Again, the desired adjustments would ordinarily be among the sorts that we discuss.

To summarize, the sorts of adjustments needed and developed for this retrospective study of death rates will be needed in future large retrospective studies in many fields and may often be useful as well in large, randomized prospective studies.

That the data on operations are gathered by means of a sample survey scarely calls for comment today. Abstracting every one of 856,000 charts in a short period would have been too expensive for this Study and would almost inevitably have led to work of poor quality or to nonparticipation by the institutions. Consequently, the use of a sample was necessary. What is a bit unusual is that data are available on essentially all the deaths. Usually, when sampling is used, nearly all the information comes from the objects sampled.

When the event of interest is rare, the information in the sample is usually more sensibly measured by the number of times the rare event happens than by the sample size. When the event occurs about half the time (say, 0.2 to 0.8), then the sample size is often a good measure because we are usually interested in accuracy as a percentage of the true value. If, however, an event occurs two times in a million trials, after noting that the event is rare we rightly feel that the rate is poorly determined; the next million might easily give zero or five occurrences--variations of 100 and 150 percent, respectively. But if an event occurs 200,000 times in a million trials, we feel that under similar conditions the next million will produce the same result within a few percent, say, 2 or 3 percent.

The strong implication of these remarks is that the information in a study of deaths after surgery is measured by the number of deaths, rather than by the number of operations. For example, a sample of 10,000 with a death rate of 1 percent is a small sample because it produces about 100 deaths; although replication under exactly equated conditions could readily produce from 80 to 120 deaths, a more realistic variation might run from 60 to 140, for a variation of 40 percent. But 40 percent would probably be about the size of difference that we would hope to detect in planning the study.

Working with retrospective data in the National Halothane Study gives an unusual advantage in that data on the deaths are fairly readily available. The cost of gathering the data on a death is much the same as that for a randomly chosen case. Because most of the accuracy in the study of the rare event, death, is contained in the deaths, we lose only modest information from sampling the 856,000 cases, rather than making a census of them. Thus, the retrospective study has a great saving. Its sample of 38,000 could have been expected to generate perhaps 760 deaths, but instead we have available the whole 17,000 deaths.

The matter of size is discussed in connection with a possible prospective study in the following section.

ON THE BASIC UNRESOLVABILITY OF VERY SMALL DIFFERENCES

In a properly randomized clinical trial, many new problems arise because the randomization does not fit the usual medical or institutional

practice. Achieving a balance in the treatments presents another problem. Should experts on treatment A handle all patients assigned to A, and experts on treatment B handle those assigned to B, or should the same persons handle both kinds of treatment? Obviously, this choice will vary with the medical problem being studied. If the same persons are to administer both treatments, there may be a need for retraining, and in any case a considerable need for cooperation. No one wants a study merely to affirm that lack of practice may give poor practice. We cannot always use experimental techniques that we prefer; for instance, in comparing anesthetics, the anesthetist rarely can be blind to his anesthetic (an exception arises when the anesthetics have nearly identical physical and pharmacologic properties, as do halothane and chloroform). All these matters make control more difficult, especially the control intended to ensure that the effect measured is the effect that occurs in the general population.

Many studies can produce definitive results even when done on a modest scale. But studies of rare events are invariably irksome, first, because of the large numbers required, and, second, because of the likely existence of sources of bias at least comparable in magnitude with the effects needing to be detected. Although the second of these considerations may be more important, the first is more easily illustrated.

As a working number, let us say that in the United States around 10 million operations are performed each year. In our study a 2 percent death rate has been observed; if this rate were applied to all operations, there would be 200,000 deaths. A slight change in the death rate, to 1.9 percent, would reduce the number of deaths by 10,000, a substantial change. What size of investigation would it take to detect reliably a difference in death rate of 0.1 percent? As a practical matter, many experienced workers would say that it could not be done with a study of any size. But, as an idealization to help guide our thinking, we can readily make some calculations to emphasize that large numbers are required.

For simplicity, suppose that we intend to compare only two treatments, the anesthetic halothane (H) and anesthetic X. Suppose further that we have no variation other than binomial. This means that, as opposed to a real situation, we will underestimate the needed sample size by an unknown amount.

Let p be the death rate after halothane and $p+\delta$ that after anesthetic X. If the death rates differ by 0.1 percent, then δ would be ± 0.001. To be confident of detecting this difference, we want the standard deviation of the observed difference to be small, say, one-sixth as big as δ, because fluctuations of two or three standard deviations in the observed difference can easily occur by chance.

When δ is small compared with p and the sample sizes for H and X are each N, the standard deviation of the difference in observed rates is about $\sqrt{2p/N}$. To meet the criterion of six standard deviations, we need $\delta/\sqrt{2p/N} = 6$, or $N = 72p/\delta^2$. For $\delta = 0.001$, $p = 0.02$, we find that $N = 1,440,000$, for a total clinical trial of 2,880,000 based on this oversimplified model. To face the more realistic difficulties requires contemplating samples several times as large as this. Obviously, before embarking on such a large-scale research program, the medical profession wants to be sure that society has a good chance of gaining much; that was the feeling, for example, toward the trial of the Salk poliovirus vaccine, which did require such a large-scale program.

In considering the extreme of a difference of 0.001, we should not overlook the drastic reduction in necessary sample size that occurs if we consider instead a difference of 0.005. Here we would need, with the simplified model, about 115,000. Such a study could perhaps be borne.

If we required δ to be a fraction of p, say, $\delta = fp$, then using the separation of 6 as before yields $N = 72/f^2p$. Consequently, for fixed f as p increases, the number required decreases. This suggests that a study restricted to operations with higher values of p might also require fewer cases and permit concentration on the portion of the surgical population especially likely to produce the deaths. But, to be realistic, we must be talking about big numbers if we are to consider the matter at all.

Let us return to the second point concerning biases. First, there is a difficulty in principle. The training, cooperation, and communication needed to carry out a huge study might very well change the small differences that we are trying to measure, so that the real differences in the untrained noncooperating institutions would not be assessed by the study. Next, just as the evidential value of a retrospective study is sensitive to the confounding of therapeutic acumen with choice of anesthetic, so is a prospective study very sensitive to slight biases of follow-up, coding decision, and so on, when directed at establishing the presence or absence of minute differences. Small studies can sometimes be handled by a staff that has a pre-existing background of effective communication, and so high standards of accuracy and uniformity can be maintained. But if a study of very great size is to be undertaken, new personnel must be trained, and the facility with which errors can be prevented, or identified and corrected, diminishes. Consequently, when one expands a sample size to reduce sampling error, he sets in motion at the same time processes that will increase nonsampling errors. (These considerations underlie the experience of the Census Bureau that a sample survey conducted by permanent staff is often more accurate than a complete enumeration for which staff must be built.)

We therefore conclude that very small quantitative differences cannot be empirically established.

Abstract of Chapter IV-2

The main purpose of the death-rate study was to find out about death rates associated with different anesthetic agents. An early task in approaching this problem was to reduce the several hundreds of different combinations of anesthetics that were administered in surgery to a small number of categories of anesthetic practice. We divided them into five groups: halothane, nitrous oxide-barbiturate, cyclopropane, ether, and "Other." The first four represented anesthetics and combinations of anesthetics that involved the named agent but not any of the other three. The category "Other" included all combinations of anesthetic agents that involved either none of the foregoing or two or more of them. The different anesthetics were used with widely varying frequency from institution to institution. Halothane was the most frequently used and ether the least.

Other variables associated with the surgical procedure have a much greater influence on survival rate than the choice of anesthetic. Such variables measured in this study include the age of the patient, the type of operation, the length of the operation, the sex of the patient, his physical status (anesthetic risk), whether the patient had had an operation in the same or the previous month, the year, and the institution.

Inevitably, some anesthetics were used more than others in particular operations, for old patients, for patients with poor physical status, etc. If these imbalances had not been corrected, they would have introduced spurious differences among the anesthetics. A way of adjusting for such interfering variables is to compute a standardized death rate. In this chapter, each interfering variable is used as a basis for computing standardized death rates. We are thus able to look at the comparisons among anesthetics purged, at least partially, of the effects of the interfering variables taken one at a time. The effect of this standardization is to enhance some differences and to reduce others. This is one indication for the need to construct standardized rates that take into account several variables at one time.

The results reported in this chapter are usually exhibited for three large subportions of the data: the high-death-rate group, which involves four different operations, about 62,000 surgical procedures, and 6300 deaths; the low-death-rate group, which involves seven very common operations, about 370,000 surgical procedures, and 800 deaths; and the middle-death-rate group, which involves the remaining 62 operations, 426,000 surgical procedures, and 9600 deaths.

The study was not designed to show death-rate differences among institutions, but dramatic differences occurred. The institutional death rates ranged from 0.0027 to 0.0641, numbers that stand in a ratio of about 1:25. Standardization on age, operation, physical status, and a composite variable called "shock-likelihood index" reduced the apparent institutional variation, but by no means eliminated it. Standardization on other interfering variables had little effect.

In summary, this chapter introduces the data of the death-rate study, exhibits the importance of several interfering variables, and gives preliminary notions of anesthetic differences after allowance for the effects of single interfering variables. The chapter also identifies two problems that call for further investigation:

(1) There is a need to compare the anesthetics after multiple adjustment for all important interfering variables.
(2) A more careful appraisal of differences among institutional death rates is called for.

CHAPTER IV-2. COMPARISON OF CRUDE AND STANDARDIZED ANESTHETIC DEATH RATES

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CLASSIFICATION OF ANESTHETIC PRACTICES AND OPERATIONS

The comparison of anesthetic agents is made somewhat complex by the fact that it is common to use several agents in the course of a single operation. In this Study, a very large number of combinations of anesthetics appeared, which was not surprising. We have defined five common anesthetic practices. The detailed definitions appear in Appendix 1, but the five anesthetic practices can be thought of, roughly, as:

(1) halothane: combinations of agents including halothane but excluding cyclopropane and ether;
(2) nitrous oxide-barbiturate: combinations of agents including nitrous oxide and thiopental but excluding halothane, cyclopropane, and ether;
(3) cyclopropane: combinations of agents including cyclopropane but excluding halothane and ether;
(4) ether: combinations of agents including ether but excluding halothane and cyclopropane; and
(5) Other: all other combinations of agents, many of which include at least two of halothane, cyclopropane, and ether; all practices using methoxyflurane or Fluoromar; and all practices that include nitrous oxide but exclude Pentothal.

Later we investigate the differences in interpretation that arise in comparing agents if the categories overlap so that any patient who received halothane is charged to halothane (even if he also received ether or cyclopropane) and simultaneously charged to any other major agent that he received.

Every operation was assigned a two-digit operation code. When the crude death rates for the different operations were examined, it was found that four had more than 1000 deaths each, and these have been treated separately as the high-death-rate operations. It was also found that seven had more than 30,000 estimated exposed each, and these have been separated out as the low-death-rate operations. The purpose of these separations was to avoid swamping the remainder of the data; the operations in those two groups were not the ones with the four highest or the seven lowest crude death rates. The high-death-rate operations are: (1) large bowel operations, (2) exploratory laparotomy, lysis of adhesions, control of hemorrhage, and drainage of abscess, (3) craniotomy, and (4) heart operations with pump. The low-death-rate operations are: (1) mouth and dental operations, (2) eye operations, (3) dilatation and curettage, etc., (4) hysterectomy, (5) herniorrhaphy, (6) cystoscopy, and (7) plastic surgery. The middle-death-rate operations involved all other specific procedures (excluding mammoplasty, for which there were no deaths and an estimated 530 operations).

The estimated numbers of procedures ("estimated exposed," abbreviated "EE") and the estimated death rates for these three groups of operations are displayed in Table 1. A very large share of the procedures and a very small share of the deaths are associated with the seven low-death-rate operations. The over-all death rate in the middle-death-rate operations is about 10 times as great as that in the low-death-rate category, and nearly 60 percent of all the deaths are in the middle-death-rate group. The high-death-rate group includes only about 7 percent of the exposures to anesthesia, but nearly 40 percent of the deaths, and the over-all death rate is nearly 50 times as great in this group as in the low-death-rate group. Comparisons of the agents with each other differ from group to group. For example, ether appears best in the low- and high-death-rate groups but not in the middle-death-rate group, Other appears to be worst in the high- and low-death-rate groups but not in the middle-death-rate group, etc.

Before attaching any significant weight at all to the agent comparisons in Table 1, it is important to recognize that many aspects of surgical procedure affect the outcome, e.g., the age of the patient, his physical condition, the operation performed on him, and its duration. If we were satisfied that all these variables were balanced equally among the five anesthetic practices, then we might take the death rates in Table 1 at face value; in fact, study of the data shows that these other variables are not equally balanced among the anesthetic agents. We must therefore examine the effects of such imbalances.

AGENT CONTRASTS ALLOWING FOR ONE VARIABLE AT A TIME

Among the variables observed in this Study that exert an important effect on mortality are: whether there has recently been a previous

TABLE 1.--AGENT COMPARISONS FOR LOW-, MIDDLE-, AND HIGH-DEATH-RATE OPERATIONS

	H	N-B	C	E	O	All
			Estimated exposed (in thousands)			
Low-death-rate operations	86.6	105.1	67.3	50.0	57.3	366.3
Middle-death-rate operations	145.7	100.8	68.1	44.2	67.2	426.0
High-death-rate operations	21.8	11.6	11.7	7.6	9.1	61.7
All operations	254.9	218.2	147.4	102.0	134.0	856.5
			Number of deaths			
Low-death-rate operations	234	209	175	63	163	844
Middle-death-rate operations	2559	1753	2397	836	2070	9615
High-death-rate operations	2064	1323	1270	492	1205	6354
All operations	4863	3292	3845	1396	3444	16840
			Death rate			
Low-death-rate operations	0.00270	0.00199	0.00260	0.00126	0.00285	0.00230
Middle-death-rate operations	0.0176	0.0174	0.0352	0.0189	0.0308	0.0226
High-death-rate operations	0.0948	0.1143	0.1086	0.0647	0.1327	0.1030
All operations	0.0191	0.0151	0.0261	0.0137	0.0257	0.0197

operation, the anesthetic risk (physical status) as judged at entrance to surgery, the duration of the operation, the patient's age, and the patient's sex. The other variables investigated--the institution, the year, and the type of operation--may also prove important. All these variables are defined in Appendix 2.

Tables EE-1 through EE-26 (at the end of this chapter) display for the different anesthetic practices* how the cases were distributed on the variables. They are followed by Tables DR-1 through DR-26, which display the death rates ("DR") by anesthetic practice and the variables.

The death rates exhibited after Table 1, generally throughout Part IV, are calculated as the quotient "deaths divided by deaths plus estimated exposed"; this is sometimes written as "D/D+EE." This estimate is somewhat unconventional, and a few words of explanation are in order here (a fuller discussion appears as Appendix 3). In a cell with few cases, it can happen (and does) that some deaths are observed although the random sample provided no cases for the cell; in that case the plausible "ordinary" estimate, D/EE, would have a zero denominator. The estimator D/D+EE yields the value 1.0 in that case. Of course, invariably the estimate we have used is smaller than the "ordinary" estimator. But if EE is large and the death rate is small, there is little difference between the values of the two estimates. In cells with both high death rates and large EE, it may be worthwhile to reconvert the estimates to D/EE form. For comparisons of death rates, however, this will rarely be useful. Interpretation of these tables and their use is illustrated by the following discussion of Tables EE-5 and DR-5.

Table DR-5 displays the death rates for each of the anesthetic practices, by category of physical status. In studying this table, one sees that the death rate depends strongly on the physical status, ranging from about one-fourth of 1 percent for physical status 1 to over 30 percent for physical status 7 (moribund). The row labeled "over-all" shows the death rates for each of the agents. The next row, labeled "standardized death rate," can be explained by reference to Table EE-5. This table shows for each of the common practices in the middle-death-rate operations the percentage of patients in each physical status category. In comparing the cyclopropane column with the "all" column, one is struck by the fact that cyclopropane has a disproportionately large share of patients in status categories 5, 6, and 7. These are very high death-rate categories. It is clear that the death rate for cyclopropane will tend to be high because it is used so often in patients in these physical status groups. The standardized death rate adjusts for this kind of imbalance. It is determined by taking the cyclopropane death rates for the various physical status categories and calculating what the over-all death rate for cyclopropane would have been if these rates had been applied to a population of the kind shown in the "all"

*Tables EE-1 through EE-26 and DR-1 through DR-26 are early computer printouts; the columns for nitrous oxide-barbiturate are labeled "NP" instead of the later abbreviation, "N-B."

column of Table EE-5. The resulting number (Table DR-5) is 0.0286, quite different from the raw value of 0.0340. The standardized rates for the other agents are similarly computed.*

In comparing the standardized rates with the over-all rates, it is seen that standardization in correcting for imbalance between agents on physical status has made halothane, nitrous oxide-barbiturate, and ether look somewhat less favorable and both cyclopropane and Other somewhat more favorable than they did before standardization. The next row of Table DR-5, "standard (ratio)," is calculated by dividing all the entries in the row above it by 0.0221, which is the crude over-all death rate, or equivalently, the standardized rate calculated by applying average death rates within risk categories to the over-all population. The figures in this row enable one to see conveniently whether an agent has a higher or lower death rate than "average."

An alternative to (direct) standardization, just described, is the computation of an "indirectly standardized mortality ratio." The objective is, again, to compare agents in a way that is corrected for disparities among the populations to which the agents were applied, but the method is different in detail. The death rates for "standard population" (in this case, the "all agents" population) are applied to the population exposed to, say, cyclopropane; this leads to a putative number of deaths, i.e., the number that "would have" occurred in the cyclopropane-treated patients if the general death rates had applied (this is a sort of par value). Then the ratio of the actual number of deaths to that par is calculated; it would exceed unity if there were excessive deaths with cyclopropane. This indirect method can still be used where some operations are not done at all with, say, cyclopropane, and the direct method cannot. (For example, if no hysterectomies were done with ether, the direct method would fail for the lack of an observed ether death rate, but the indirect method would work, both par and observed deaths being zero.) This illustrates the advantage that can accrue with the indirect method. Generally, in our study the two approaches lead to conclusions that agree closely. The bottom row of Table DR-5 shows this indirectly standardized mortality ratio.

Tables EE-1 through EE-26 all show percentage distributions of the patients assigned to the anesthetic practices with respect to the interfering variables (risk, etc.). The percentages in each column therefore add (approximately) to 100. The bottom row of each table gives the total numbers of estimated exposures in the anesthetic practices expressed in thousands.

*Detailed formulas used in these calculations appear in Appendix 4. The weights used are based on D+EE, rather than EE, because the death rates have denominators of the D+EE type, rather than the EE type.

The Tables of Estimated Exposures

Previous Operation

This variable has three classes. The great bulk of the procedures were performed on patients who had had no previous surgery in either the month of the surgery relevant to this Study or the month before. Only 7.5 percent of the cases in the low-death-rate group, 10.3 percent in the middle-death-rate group, and 14.3 percent in the high-death-rate group had had a previous operation. Cases in which there had been a previous operation were classified according to whether halothane was used then or not. A striking but not surprising feature is that the fraction of patients who received halothane for previous operations was far greater in the halothane population than in any of the others.

Physical Status

In the low-death-rate operations there was a marked tendency for cyclopropane to be used relatively more often in emergency operations (physical status 5, 6, and 7) than any of the other anesthetic agents, and for ether to be used far less in emergency operations. The findings were similar, although not quite so marked, in the middle- and high-death-rate groups.

Length

From low- through middle- to high-death-rate operations, there was a striking increase in the fractions of longer procedures. In the low-death-rate group, nitrous oxide-barbiturate was used more than the other agents. In the middle-death-rate operations, ether had more than its share of long procedures; and in the high-death-rate operations, both cyclopropane and ether had less than their shares of long procedures.

Age

In the low-death-rate group, both ether and Other were used very heavily for children and ether was used more heavily than the other agents in the 10-19 age group. In the middle-death-rate operations, ether and Other were again used relatively more for children. In the high-death-rate group, Other had a disproportionately high share of administrations to children.

Sex

In the low-death-rate operations, cyclopropane and nitrous oxide-barbiturate were used in females in far greater than ordinary proportions. This is probably a reflection of the heavy use of both in dilatation and curettage and of cyclopropane in hysterectomy. In the middle-death-rate

operations, there was some tendency for cyclopropane and nitrous oxide-barbiturate to be used more in females. But there were no clear sex effects at all for the high-death-rate operations.

Year

There was a marked increase in the use of halothane over the period 1959-1962, compensated primarily by a decrease in the use of nitrous oxide-barbiturate and ether, although cyclopropane also showed a downward trend over that period.

Institution

The most notable feature of the hospital distribution of the different anesthetic agents is the diversity of usage patterns. The number of hospitals responsible for as few as 1 percent of all the operations that involved halothane (in the whole Study) is less than the number responsible for so few cases involving any of the other agents. At the other extreme, over half the hospitals were each responsible for fewer than 1 percent of all the operations that involved ether. Indeed, three institutions (1, 8, and 9) together accounted for 49.5 percent of the low-death-rate operations that involved ether; and institutions 8 and 9 together accounted for 53.4 percent and 50.0 percent of the ether operations in the middle- and high-death-rate groups, respectively.

To study usage patterns further by institution, it is convenient to assemble all the operations. This is done in Table EE-22. This table has been constructed so that it shows what percentage of each hospital's operations involved each anesthetic practice. Thus, each row of this table adds to 100 percent, whereas in the other EE tables the columns add to 100 percent. This table shows the great diversity in the popularity of the agents.

Halothane was the most commonly used agent in the entire Study, and it was also the most commonly used in 17 individual institutions. Only in institution 20 was it the least commonly used agent. The over-all use of halothane was about 30 percent, but its use in individual hospitals ranged from about 6 percent to nearly 63 percent. Nitrous oxide-barbiturate, the second most commonly used agent in the entire Study, was used more commonly than all the other agents in six institutions, and was the least used agent in one institution; its percentage of use ranged from 1.9 to 73.3. Cyclopropane, ranking third in over-all use, presented a very heterogeneous use pattern from institution to institution, from 0.2 to 48 percent. In seven institutions it was the most commonly used agent, and in eight the least commonly used. Ether had the lowest over-all use, 11.9 percent. In 22 institutions it was less used than all the other agents, but in two it was the most commonly used; its percentage of use ranged from 0 to 38.5. The use of Other ranged from 2.1 to 41.4 percent; it was the most commonly used in two institutions and the least commonly used in three.

Operation

The operation tables are the only ones in which the labels of the rows are different for the low-, middle-, and high-death-rate groups. The seven low-death-rate operations show quite different patterns as to the agents used. Ether and Other are prominent for the mouth operations (code 1). Nitrous oxide-barbiturate was very commonly given for dilatation and curettage (code 60) and for cystoscopy (code 73). Cyclopropane was very commonly used for dilatation and curettage (code 60) and for hysterectomy (code 65). The names (or codes) of the middle-death-rate operations are not shown; the 25 rows correspond to collections of operations that were grouped in such a way that the death rate steadily increases with the group number. For these operations halothane was more commonly used than any other agent, and ether least. Halothane was also the most commonly used and ether the least commonly used in the high-death-rate operations. In fact, halothane was used in almost twice as many procedures as its nearest competitor. Ether was never used in operation 33 (heart with pump), and cyclopropane was almost never used in operation 12 (craniotomy) and only rarely in operation 33.

The Tables of Death Rates

Tables DR-1 through DR-26 display death rates (estimated as D/D+EE) for the various anesthetic agents and the interfering variables. The crude over-all death rate for each agent is shown, together with the death rate standardized on the all-agents population for the variable under consideration. The standardized death rate is also exhibited in the ratio form, and the indirectly standardized mortality ratio is given for each agent.

Previous Operation

Death rates were much higher if there had been a previous operation than if there had not; that was true in the low-, middle-, and high-death-rate groups. In the low- and middle-death-rate groups little difference in death rate was associated with the distinction between previous operations with and without halothane. In those groups, standardizing with respect to previous operation has little effect, leading to rates hardly different from the crude rates. In the high-death-rate group, the death rates were lower if halothane had been used in a previous operation (than if it had not) for two of the agents (halothane and Other), and higher for the other three agents. Standardization has a small effect, and does not alter the rank order of the death rates.

Physical Status

Physical status has a very strong association with death rate. In the low-death-rate group, the rate changes from 0.0004 to 0.0565 in the non-emergency operations; the effect of standardizing with respect to physical status is to cause ether to look less advantageous and Other to look even worse. In the middle-death-rate group, a similarly strong gradient is seen, and the effect of standardization is to reduce the apparent inferiority of cyclopropane, as well as that of Other. In the high-death-rate group, there is again a marked gradient, and the effect of standardization is to reduce greatly the apparent superiority of ether and to reverse the standings of cyclopropane and halothane, the latter appearing worse.

Length

Length is another variable that has a profound association with death rate. In the low-death-rate group, the shortest operations had a death rate of less than 0.1 percent, and the longest operations more than 2 percent. The only important contrast among the death rates standardized with respect to length is the markedly lower rate associated with ether. In the middle-death-rate group, the gradient with length ranges from 0.6 percent to almost 11 percent; after standardization, ether, halothane, and nitrous oxide-barbiturate look about equally good. In the high-death-rate group, the regularity of the gradient with length is not so clear. Short operations (up to 28 min) had the lowest death rate, but there is no strong or clear gradient between 0.5 and 4 hr; when operations were longer than that, the death rate rose with length. The effect of standardization in the high-death-rate operations is primarily to make cyclopropane and Other look worse.

Age

For all three groups of operations, the death rate was higher for the patients 0-9 years old than for young adults, and increased steadily with age beginning at 10 years. In the low-death-rate group, standardization with respect to age raises the death rates for cyclopropane and Other rather substantially; in the middle-death-rate group, standardization has little effect; and in the high-death-rate group, standardization hardly changes the rates and does not change their rank order, but there is a modest increase for nitrous oxide-barbiturate.

Sex

In all three groups, the death rates for males were higher than for females: in the low-death-rate group, 0.003 and 0.002 respectively; in the middle-death-rate group, 0.027 and 0.017; and in the high-death-rate group, 0.104 and 0.083. Standardization with respect to sex results in little modification of death rates, except that it substantially increases the rate for cyclopropane in the low-death-rate group.

Year

There was no important regular variation in death rate with year, and standardization for this variable has little effect.

Institution

Death rates for institutions exhibit large and important variability. In the low-death-rate group, three institutions (1, 21, and 28) had death rates under 0.1 percent, and three institutions (24, 25, and 30) had death rates over 1 percent. The range of death rates over the 34 institutions for the low-death-rate operations was from 0.0005 to 0.0141. In the middle-death-rate group, one institution (28) had a death rate under 0.0050, and three (2, 7, and 25) had death rates over 0.0500. In the high-death-rate group, three institutions (14, 21, and 28) had death rates under 0.0600, and seven (2, 5, 7, 24, 25, 29, and 31) had death rates over 0.1300; the range in the high-death-rate group was from 0.024 to 0.160. The over-all crude death rates for all groups ranged from 0.0027 to 0.0641, with six institutions (1, 3, 14, 17, 23, and 28) having death rates under 0.0100, and three institutions (2, 24, and 25) having death rates over 0.0600.

Comparison among the crude death rates by anesthetic agent in the various institutions presents a confused picture. For example, although cyclopropane had the highest crude death rate, in nine institutions the cyclopropane rate was below the over-all rate. Other had the second highest crude death rate, but in eight institutions its death rate was lower than the over-all death rate. Ether had the lowest over-all crude death rate, but in nine institutions the ether death rate was higher than the over-all death rate--and in two it was not used at all.

The effect of standardizing the agent death rates with respect to institution is generally to raise the rates; this happens for each agent in each group, except halothane in the low-death-rate group. This phenomenon is presumably a result of there being an average tendency for high death rates to accompany an anesthetic agent used only infrequently in a hospital; when such rates are applied to the (larger) general-usage fraction, a large contribution to the standardized death rate results. Similarly, a much-used agent in a particular hospital may have a lower death rate than usual, but if the low rate is applied to the (smaller) general-usage fraction, this will also tend to make the standardized death rate larger than the observed one. The indirectly standardized mortality ratio seems a better index for standardization with respect to institution. (Indeed, institution is one of the very few variables for which there is much difference between the two approaches.) In the low-death-rate group, standardization (indirect) does not greatly change

the comparison among agents from that indicated by the crude rates. In the middle-death-rate group, the positions of cyclopropane and Other are reversed by standardization (indirect), and the apparent virtue of ether is much reduced at the same time. In the high-death-rate group, standardization (indirect) alters the interpretation but little; nitrous oxide-barbiturate, which has a slightly higher crude rate than cyclopropane, now seems slightly superior to cyclopropane.

Operation

In the low-death-rate group, there was substantial variability in the death rates by operation, from 0.00066 to 0.00689. Ether appears to be markedly the best of the agents in this group, although standardization with respect to operation somewhat reduces its apparent superiority and at the same time causes halothane to look better than before and cyclopropane and Other to look worse. In the middle-death-rate group, the gradient of over-all death rate with operation subgroup number is obvious. The effect of standardization in this group is not very large, although it does alter the relative positions of halothane, nitrous oxide-barbiturate, and ether. In the high-death-rate group, there was great variability in the death rates for the four operations (ranging from 0.0565 to 0.1601), and the effects of standardization are large. In terms of indirect standardized mortality ratios, ether and halothane appear to be best and about equally good.

Tables EE-26 and DR-26 provide a more detailed breakdown of the data by operation. These tables show the operations by operation code.

The table of estimated exposures shows some interesting patterns. First, halothane was the least used for certain "pet" operations. For each of nitrous oxide-barbiturate, cyclopropane, and ether, there are two operations that together accounted for some 30 percent of the administrations: for nitrous oxide-barbiturate, operation 60 (20.5 percent) and operation 73 (10.8 percent); for cyclopropane, operation 60 (21.5 percent) and operation 65 (8.8 percent); and for ether, operation 1 (24 percent) and operation 65 (6.4 percent). This usage concentration was less marked for Other; the two commonest operations together account for only 22.1 percent of the administrations: operation 1 (16.7 percent) and operation 55 (5.4 percent). But with halothane, the two commonest operations together accounted for less than 14 percent: operation 1 (6.5 percent) and operation 60 (6.9 percent). Second, inspection of the number of operation codes for which the individual agents were very rarely used shows that halothane was the most widely used. Any operation listed in the table of estimated exposures for which an agent shows 0.0, 0.1, or 0.2 is one for which the agent was used in less than one-fourth of 1 percent of all administrations of that agent. The frequencies of such "avoided" operations are (not counting "unknown" operations): halothane, 17; nitrous oxide-barbiturate, 19; cyclopropane, 27; ether, 21; and Other, 20. In fact, five of the operations are "rare," in that they show 0.0 for all five agents. If these are omitted from the count, the figures become: halothane, 12; nitrous oxide-barbiturate, 14; cyclopropane, 22; ether, 16; and Other, 15. In the sense of having the fewest "avoided" operations, halothane is the most widely used in this body of data. (This is not because it was used most often of the agents; the discussion is in terms of the percentage of the times the agent was used, and each agent was on an equal footing: its own 100 percent was disposed onto 76 + "unknown" operations.)

Table DR-26 shows the death rates for the different operations, by anesthetic agent. (Here we see some instances of deaths occurring where estimated exposed is zero: operation 43 for nitrous oxide-barbiturate and operation 33 for ether both had death rates of 1.00000.) The death rates ranged from 0.00000 for operation 31 (an ill-determined rate) to 0.16012 for operation 33. Several operations had death rates under 0.001, and several over 0.120. The data are complex; standardization with respect to operation removes much of the variation among agent death rates, and changes the rank order of death rates greatly, chiefly as a result of ether's having the smallest crude rate and the largest standardized rate. In terms of the indirect mortality ratio (probably a more appropriate index here), there is much less change from the pattern of the crude death rates.

Tables 2, 3, and 4 summarize the standardized death rates and direct mortality ratios for the low-, middle-, and high-death-rate groups exhibited in Tables DR-1 through DR-26. In Table 2, we see that Other has the highest or next highest standardized death rate among the agents in every row; that ether and nitrous oxide-barbiturate always have the two lowest standardized death rates, in an order depending on what has been standardized for; and that halothane and cyclopropane are always in third, fourth, or fifth positions, again depending on what has been standardized for. Furthermore, there is good quantitative agreement between corresponding standard mortality ratios and indirectly standardized mortality ratios, with one notable exception: standardizing for institution produces very different ratios for cyclopropane (direct, 2.151; indirect, 0.981) and for Other (direct, 1.779; indirect, 1.324).

In the middle-death-rate group (Table 3), there is much more uniformity. Cyclopropane always has the highest standardized rate, Other always the next highest, and halothane and nitrous oxide-barbiturate ordinarily the two lowest positions, with ether third, except when the standardization is with respect to length or operation. As was the case with the low-death-rate operations, there is good quantitative agreement between the direct and indirect mortality ratios, except for standardization with respect to institution, for

TABLE 2.--AGENT-STANDARDIZED DEATH RATES ON "ALL AGENTS" POPULATION
(Low-Death-Rate Operations)

Standardizing variable	Standardized death rate					Direct mortality ratio					Indirect mortality ratio				
	H	N-B	C	E	O	H	N-B	C	E	O	H	N-B	C	E	O
Previous	0.00258	0.00201	0.00263	0.00123	0.00293	1.124	0.875	1.146	0.536	1.274	1.088	0.885	1.142	0.572	1.260
Physical status	0.00264	0.00192	0.00235	0.00210	0.00349	1.149	0.835	1.024	0.912	1.517	1.081	0.836	0.968	0.733	1.470
Length	0.00247	0.00235	0.00275	0.00114	0.00268	1.076	1.022	1.194	0.495	1.164	1.078	1.036	1.156	0.488	1.125
Age	0.00264	0.00175	0.00333	0.00192	0.00381	1.147	0.761	1.450	0.834	1.656	1.109	0.715	1.276	0.715	1.415
Sex	0.00265	0.00209	0.00300	0.00132	0.00279	1.151	0.908	1.306	0.576	1.212	1.145	0.888	1.200	0.521	1.186
Year	0.00290	0.00191	0.00260	0.00129	0.00284	1.261	0.832	1.130	0.560	1.236	1.181	0.859	1.127	0.547	1.234
Institution	0.00269	0.00233	0.00494	0.00137	0.00409	1.168	1.015	2.151	0.596	1.779	1.096	0.907	0.981	0.639	1.324
Operation	0.00228	0.00200	0.00306	0.00147	0.00329	0.994	0.870	1.331	0.639	1.433	1.014	0.881	1.214	0.583	1.316

TABLE 3.--AGENT-STANDARDIZED DEATH RATES ON "ALL AGENTS" POPULATION
(Middle-Death-Rate Operations)

Standardizing variable	Standardized death rate					Direct mortality ratio					Indirect mortality ratio				
	H	N-B	C	E	O	H	N-B	C	E	O	H	N-B	C	E	O
Previous	0.01750	0.01745	0.03483	0.01849	0.02898	0.793	0.791	1.578	0.838	1.313	0.787	0.779	1.581	0.846	1.284
Physical status	0.01943	0.01941	0.02855	0.02119	0.02532	0.880	0.879	1.293	0.960	1.147	0.871	0.871	1.223	0.919	1.154
Length	0.01736	0.01809	0.03551	0.01648	0.03069	0.787	0.820	1.609	0.747	1.390	0.779	0.802	1.599	0.729	1.382
Age	0.01831	0.01701	0.03405	0.01838	0.02820	0.830	0.771	1.543	0.833	1.278	0.820	0.766	1.535	0.826	1.266
Sex	0.01714	0.01727	0.03513	0.01835	0.02955	0.776	0.783	1.592	0.832	1.339	0.772	0.779	1.600	0.826	1.345
Year	0.01724	0.01717	0.03419	0.01898	0.02988	0.781	0.778	1.549	0.860	1.354	0.790	0.761	1.548	0.830	1.365
Institution	0.01879	0.01790	0.04441	0.02994	0.03488	0.851	0.811	2.012	1.356	1.580	0.796	0.757	1.317	1.054	1.405
Operation	0.01857	0.02080	0.03004	0.01819	0.02793	0.841	0.942	1.361	0.824	1.265	0.828	0.906	1.320	0.741	1.257

TABLE 4.--AGENT-STANDARDIZED DEATH RATES ON "ALL AGENTS" POPULATION
(High-Death-Rate Operations)

Standardizing variable	Standardized death rate					Direct mortality ratio					Indirect mortality ratio				
	H	N-B	C	E	O	H	N-B	C	E	O	H	N-B	C	E	O
Previous	0.08763	0.10401	0.10168	0.06091	0.11661	0.939	1.114	1.089	0.653	1.249	0.929	1.114	1.052	0.616	1.282
Physical status	0.09467	0.09832	0.09254	0.07787	0.10494	1.014	1.053	0.991	0.834	1.124	0.988	1.072	0.966	0.777	1.112
Length	0.08237	0.09440	0.11011	0.07978	0.12364	0.882	1.011	1.179	0.855	1.324	0.876	1.011	1.172	0.689	1.351
Age	0.08907	0.10887	0.09704	0.06010	0.11906	0.954	1.166	1.039	0.644	1.275	0.949	1.140	1.028	0.614	1.228
Sex	0.08641	0.10279	0.09804	0.06096	0.11693	0.926	1.101	1.050	0.653	1.253	0.920	1.114	1.056	0.630	1.285
Year	0.09121	0.10541	0.09822	0.06103	0.11758	0.977	1.129	1.052	0.654	1.259	0.955	1.074	1.058	0.610	1.264
Institution	0.08845	0.11781	0.14317	0.13107	0.13645	0.946	1.261	1.532	1.403	1.460	0.956	0.989	1.011	0.716	1.318
Operation	0.07763	0.09251	0.11184	0.20216	0.12370	0.832	0.991	1.198	2.166	1.325	0.849	1.036	1.245	0.745	1.249

which the direct ratios are much higher than the indirect for both cyclopropane and ether.

In the high-death-rate group (Table 4), there is also considerable uniformity, best seen in the indirect ratios, where, for each standardization, ether has the lowest ratio and Other the highest. For all standardizations except with respect to physical status, halothane is second; and nitrous oxide-barbiturate and cyclopropane are usually third and fourth. All these statements hold true for both standardized death rates and direct mortality ratios, except for standardization with respect to institution and operation, where ether has high direct mortality ratios and the lowest indirect ratios, and other inversions occur.

INVESTIGATION AND DISCUSSION OF INSTITUTIONAL VARIATION IN DEATH RATES

One of the interfering variables that has been very influential in affecting agent comparisons is the institution. Review of Tables 2, 3, and 4 shows that standardization for institution sometimes leads to results that are at variance with those obtained by standardization for other variables. Standardization for institution could be expected to have peculiar effects, inasmuch as there are marked variations in death rates from hospital to hospital, marked differences in the degrees of use of the anesthetic agents, and, presumably, rather sharply different kinds of

TABLE 5.--STANDARDIZED MORTALITY RATIOS FOR 34 INSTITUTIONS
(All Operations)

Institution	D/D+EE	Ind. S.M.R.	Previous operation	Physical status	Sex	Year	Operation	Age	Shock likelihood
1	0.00732	0.374	0.404	0.524	0.386	0.373	0.716	0.443	0.523
2	0.06049	3.274	3.404	1.062	3.417	3.306	2.577	2.629	1.975
3	0.00803	0.411	0.440	1.059	0.411	0.407	0.688	0.420	0.842
4	0.02394	1.247	1.224	0.773	1.294	1.240	1.149	1.307	1.120
5	0.03512	1.851	1.835	1.411	1.862	1.851	1.620	1.856	1.236
6	0.01085	0.558	0.562	0.602	0.597	0.558	0.974	0.595	0.724
7	0.04532	2.414	2.398	1.498	2.414	2.458	2.309	1.956	1.762
8	0.01456	0.751	0.743	0.926	0.724	0.754	0.577	0.645	0.757
9	0.01730	0.895	0.849	0.924	0.877	0.892	0.897	0.912	0.963
10	0.02661	1.390	1.358	1.122	1.361	1.384	1.115	1.231	1.476
11	0.02070	1.075	1.008	0.659	1.046	1.072	0.887	1.309	0.992
12	0.01966	1.019	1.023	1.709	1.055	1.013	0.976	1.000	1.083
13	0.03447	1.815	1.883	4.307	1.370	1.857	0.979	1.670	1.367
14	0.00518	0.264	0.280	0.274	0.266	0.263	0.472	0.321	0.274
15	0.01899	0.984	1.005	1.118	1.026	0.982	1.223	0.992	0.941
16	0.03128	1.642	1.641	1.408	1.610	1.631	1.086	1.728	1.148
17	0.00933	0.478	0.421	0.505	0.436	0.485	0.557	0.830	0.549
18	0.03544	1.868	1.935	0.953	1.895	1.870	1.109	1.611	1.145
19	0.02583	1.348	1.355	1.471	1.372	1.352	1.121	1.275	1.418
20	0.01507	0.778	0.783	0.838	0.810	0.779	0.973	0.741	0.754
21	0.01235	0.636	0.664	0.961	0.640	0.636	0.627	0.593	0.627
22	0.01932	1.002	0.999	0.916	1.042	0.996	1.301	1.061	1.198
23	0.00842	0.431	0.472	0.720	0.447	0.434	0.651	0.542	0.615
24	0.06340	3.442	3.270	2.122	3.334	3.461	1.477	3.067	1.899
25	0.06405	3.480	3.280	1.817	3.374	3.503	2.413	1.968	2.268
26	0.01030	0.529	0.533	0.782	0.543	0.525	1.036	0.571	0.839
27	0.01074	0.552	0.563	1.018	0.561	0.555	0.780	0.623	0.723
28	0.00268	0.136	0.148	0.348	0.136	0.137	0.287	0.243	0.203
29	0.04185	2.221	2.064	1.324	2.141	2.243	1.121	2.435	1.257
30	0.04816	2.573	2.178	0.880	2.433	2.589	0.935	3.521	1.291
31	0.01421	0.733	0.747	1.662	0.730	0.731	1.261	0.773	1.363
32	0.01746	0.903	0.929	1.086	0.909	0.897	0.845	0.891	0.861
33	0.02476	1.291	1.203	0.731	1.232	1.299	1.015	1.193	1.045
34	0.01561	0.806	0.827	1.346	0.797	0.808	1.122	0.836	1.030
TOTAL	0.01928	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Maximum ratio among institutions		25.4	22.9	15.6	25.1	25.5	9.0	12.6	11.1

patient populations. Further investigation of institutional differences should be illuminating. In Table DR-22, it was seen that death rates by institution (for all operations) ranged from 0.0027 to 0.0641. This approximately 25-fold variation is, in itself, important and provocative. This section is addressed to studying institutional variation in death rate more carefully. (It is studied further in the last section of Chapter IV-6.)

Generally, the institutions differ from one another as to age distribution of patients, kinds of operations performed, etc. Thus, it is inevitable that some of the institutional variation in death rate is properly ascribed to differences in such interfering variables. A way of adjusting for these interfering variables is to compute for each institution an indirectly standardized mortality ratio for any particular interfering variable, e.g., age, sex, and operation. This has been done, and the results are summarized in Table 5.

The extreme left-hand column identifies the institutions by their code numbers. The next column gives the over-all death rate (all operations) for each institution. The next column, headed "Ind. S.M.R.," gives the indirectly standardized mortality ratio for each institution. If such a ratio is less than unity, the institution's death rate was less than the "par" value computed for its population using the entire Study's death rates for the standardizing variable; if it is higher than unity, the institution's death rate was higher. Each of the next seven columns shows the mortality ratio for the death rates of each institution standardized with respect to a single variable. If the entire difference in institutional death rates were ascribable to differences in age distribution of patients, this would cause all the mortality ratios in the column headed "Age" to be 1.000. Variation among the ratios in that column reflects institutional variation not associated with age distribution. Other columns are analogously interpreted.

Study of Table 5 shows that standardization with respect to physical status, age, operation, and shock-likelihood index (SLI)* each substantially reduces the institutional variation, but standardization with respect to previous operation, sex, and year each has very little effect. A rough-and-ready index of variation among the mortality ratios is the ratio of the highest number in the column to the lowest. These figures are displayed in the bottom row of the table. Standardization for operation has the greatest effect of all; the smallest standardized mortality ratio is 0.287 (institution 28) and the largest is 2.577 (institution 2). This is a 9-fold range, which, although smaller than the original 25-fold range, is still large. Our conclusion from Table 5 is that some, but by no means all, of the institutional variation in death rates is ascribable to the interfering variables age, operation, and physical status. The part that is not stands as an unsolved problem.

ADJUSTMENT FOR MORE THAN ONE VARIABLE AT A TIME

Two features of the preceding presentation deserve comment. First, the entire body of data has been summarized into three groups--the low-, middle-, and high-death-rate operations--rather than fractionated into many small, independently meaningful subclasses. Second, contrasts among the agents have been examined after adjustment for each of several interfering variables, but these adjustments have all been made for one variable at a time.

Such an analysis fails to reveal many aspects of the data. It does not answer such questions as: "How do the agents compare for people 30 to 50 years old who undergo nonemergency cholecystectomies?" Many questions of this kind could be posed, and the experience of this Study can give reasonable answers to some. This approach to analysis is elaborated in considerable detail in Chapter IV-3. Over-all summaries of the kind presented above occasion different answers, depending on which interfering variable is adjusted for. This variety in over-all answers is troublesome and invites a search for methods to adjust for all variables simultaneously.

Comparison of death rates by anesthetic agent after adjusting for all the identified interfering variables, simultaneously, poses difficulties. In principle, it would appear that the complete pigeonhole array of all possible combinations among the variables could be set forth, and standardized death rates for each agent calculated using the agent death rates and the population belonging to each of the many pigeonholes. Unfortunately, this procedure is not practical if 10 ages (or even seven), 25 operations (or even five), five lengths of operation, seven levels of physical status (or even four), two sexes, and two classes for previous operation are used. It is not practical because there are too many ill-defined agent death rates and cell frequencies involved in a table with so many pigeonholes, compared with the number of observations.

There are several basic ways of trying to take account simultaneously of all these interfering variables. One way is to condense the classifications greatly so that the over-all set of pigeonholes has a relatively small number of cells; for example, if the six variables above were all dichotomized, there would be only 64 pigeonholes, a manageably small number. A second way is to fit a model (e.g., regression or a parameterized multinomial) that involves all the interfering variables and the agents; then the estimates of the parameters for agent effects could be studied. A third way is to fit a model using the interfering variables (but ignoring agent) to establish strata graduated with regard to mortality; for example, the top stratum might involve a few extremely serious operations and very old, high-risk patients in certain less-serious operations, etc., and the lowest stratum might involve all subjects on some very trivial operation, and young, low-risk subjects with short operations or certain not-quite-trivial operations, etc.; once the strata have been established, the standardized death rates for the various agents can be calculated and compared.

Most of the approaches just sketched have been applied in Part IV in one or more ways. In Chapter IV-3, the analysis is addressed primarily to making adjustments for several variables simultaneously so that death rates can be compared at the level of single cells. In addition, the fitting process used for that purpose does enable construction of strata, homogeneous as to fitted death rate, and thus agents can be compared after standardization with respect to these strata. This is done in a part of Chapter IV-5. In Chapter IV-6, the anesthetic agents are compared in terms of standardized death rates and indirect mortality ratios, with standardization based on strata that were constructed by coalescing cells of the various cross-classifications in order of observed (rather than fitted) death rates. Chapter IV-5 compares the agents in a similar way; the only difference is that the strata were constructed by coalescing cells of various cross-classifications in order of estimated death rates as fitted by a multiple-regression approach. The methods of Chapter IV-4 may be thought of as partaking something of both cell aggregation and regression methods. These three chapters (IV-4, -5, and -6) all construct "strata" with a view to dividing the data into subgroups of relatively homogeneous death rates, which enable agents to be compared

*SLI is a composite variable determined by operation and physical status; a detailed definition of it is given in Chapter IV-7.

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(by standardization), with the influence of all other relevant variables largely controlled through the stratification.

This discussion has used the word "stratification" in a not very usual sense, which deserves remark. Ordinarily, strata consist of identifiable sub-parts of a population that can be identified without reference to the value of the random quantity being studied. For example, in studying income, we can use occupations as strata and we know a person's stratum before we find out his income. In the present context, we have set up the "strata" in terms of what the death rate turned out to be. This is where the difference lies. In all these stratification processes,* we have ignored the anesthetic agents, so that the stratification schemes have been "blind to the agents." All these approaches, where the "strata" depend on the observed death rates, present theoretical problems, whose full understanding still awaits research not done.

Where only a single variable has been adjusted for, the categories of that single variable have defined "strata" in the classical sense of the word. The only instance in which two or more variables have been simultaneously used to yield "strata"--in the classical sense--for standardization of agent death rates is in Chapter IV-7, where the composite variable, SLI, yields the strata, and where that composite variable is an a priori combination of operation and physical status. It should be added that the composite variable, SLI, has also been treated in the sequel as one of several variables by such methods as smear and sweep, cell aggregation, and regression.

*An exceptional instance arises in Chapter IV-5.

TABLE EE-1

PREVIOUS OPERATION vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
NO PREVIOUS OP	89.8	93.3	92.9	94.0	93.2	92.5
NO HALOTHANE	3.9	5.5	5.9	5.4	4.8	5.1
HAD HALOTHANE	6.3	1.2	1.2	.6	2.1	2.4
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-2

PREVIOUS OPERATION vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
NO PREVIOUS OP	90.3	90.7	90.9	90.7	84.6	89.6
NO HALOTHANE	4.9	8.1	7.9	8.3	12.1	7.6
HAD HALOTHANE	4.8	1.2	1.3	1.0	3.2	2.7
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-3

PREVIOUS OPERATION vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
NO PREVIOUS OP	85.9	87.2	86.2	83.3	84.6	85.7
NO HALOTHANE	6.6	11.5	12.8	15.4	10.7	10.4
HAD HALOTHANE	7.4	1.3	.9	1.3	4.7	3.9
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-4

PHYSICAL STATUS vs AGENT -- ESTIMATED EXPOSED (LOW)

PERCENT DISTRIBUTION WITHIN COMMON PRACTICE

	H	NP	C	E	O	ALL
UNKNOWN	14.2	15.8	15.8	15.3	15.2	15.3
RISK 1	58.9	57.9	56.9	69.1	66.1	60.7
RISK 2	19.0	18.9	14.5	12.5	13.1	16.3
RISK 3	3.7	3.3	2.6	2.3	2.7	3.0
RISK 4	.4	.2	.4	.0	.1	.2
RISK 5	3.0	3.3	8.2	.5	2.2	3.6
RISK 6	.8	.6	1.5	.2	.6	.8
RISK 7	.0	.0	.0	.0	.0	.0
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-5

PHYSICAL STATUS vs AGENT -- ESTIMATED EXPOSED (MID)

PERCENT DISTRIBUTION WITHIN COMMON PRACTICE

	H	NP	C	E	O	ALL
UNKNOWN	16.2	16.3	14.9	16.3	17.7	16.2
RISK 1	45.0	46.1	40.2	45.8	37.9	43.5
RISK 2	25.2	24.7	20.7	24.4	26.0	24.4
RISK 3	6.1	6.8	5.6	8.2	9.1	6.9
RISK 4	.8	.6	1.0	.5	1.2	.8
RISK 5	4.5	3.3	11.0	2.9	4.4	5.1
RISK 6	1.8	1.9	5.6	1.6	3.0	2.6
RISK 7	.3	.3	1.1	.4	.6	.5
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-6

PHYSICAL STATUS vs AGENT -- ESTIMATED EXPOSED (HIGH)

PERCENT DISTRIBUTION WITHIN COMMON PRACTICE

	H	NP	C	E	O	ALL
UNKNOWN	16.0	12.6	15.1	10.6	20.5	15.2
RISK 1	21.7	17.2	18.0	25.9	15.5	19.8
RISK 2	31.8	34.1	29.1	39.8	28.9	32.3
RISK 3	17.4	19.4	11.9	12.5	15.4	15.8
RISK 4	3.6	4.0	2.8	1.9	1.9	3.1
RISK 5	5.2	4.1	9.0	3.1	4.5	5.3
RISK 6	3.5	7.6	11.5	5.9	10.3	7.1
RISK 7	.8	1.0	2.4	.3	2.9	1.4
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-7

LENGTH vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.3	.3	.1	.0	.2	.2
1-28 MIN	16.8	31.8	26.8	9.4	12.8	21.3
29-58	33.3	37.7	32.0	37.5	38.5	35.7
59-118	31.6	20.4	22.1	34.8	29.8	26.8
119-238	15.8	8.6	17.5	15.9	16.4	14.2
239-388	2.1	1.0	1.3	2.2	1.9	1.6
389 UP	.2	.2	.0	.2	.3	.2
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-8

LENGTH vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.5	.0	.0	.4	1.2	.4
1-28 MIN	5.6	8.0	3.9	2.7	13.8	6.9
29-58	17.5	22.3	18.3	11.9	15.0	17.8
59-118	32.7	29.5	37.5	30.3	29.5	31.9
119-238	33.7	28.5	30.8	41.2	28.8	32.0
239-388	8.6	10.3	8.1	11.4	9.9	9.4
389 UP	1.4	1.3	1.4	2.3	1.9	1.6
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-9

LENGTH vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.3	.1	.1	.0	.3	.2
1-28 MIN	.9	.3	.6	.0	1.4	.7
29-58	2.1	5.3	6.0	4.5	3.5	3.9
59-118	19.0	15.8	31.2	30.1	19.1	22.1
119-238	37.4	33.1	44.5	43.5	46.0	39.9
239-388	28.6	30.3	15.6	20.0	25.2	24.9
389 UP	11.7	15.0	2.1	2.0	4.6	8.2
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-10

AGE vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.2	.0	.1	.0
0-9	20.7	2.6	12.1	55.4	52.7	23.7
10-19	9.7	7.8	5.7	11.3	7.3	8.3
20-29	12.4	17.4	18.6	5.3	6.4	13.1
30-39	16.0	21.9	21.4	8.5	8.7	16.5
40-49	15.1	18.9	21.2	7.1	9.7	15.4
50-59	11.7	14.3	11.2	5.5	6.6	10.8
60-69	10.1	11.1	6.7	4.4	4.6	8.1
70-79	3.2	4.6	2.4	1.9	3.0	3.3
80-89	.7	1.3	.3	.5	.7	.8
90 UP	.2	.0	.0	.0	.0	.0
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-11

AGE vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.1	.0	.1	.0
0-9	10.5	2.9	6.7	15.6	18.9	9.9
10-19	10.9	9.4	8.1	8.0	8.5	9.4
20-29	9.9	12.5	13.6	9.3	8.1	10.8
30-39	13.9	14.6	16.1	11.9	11.9	13.9
40-49	17.2	19.3	16.9	17.2	14.4	17.2
50-59	16.5	17.0	14.7	15.8	15.7	16.2
60-69	14.2	14.6	14.8	14.5	13.3	14.3
70-79	5.8	7.5	6.7	6.4	7.2	6.6
80-89	1.1	2.1	2.1	1.1	1.8	1.6
90 UP	.0	.0	.2	.0	.1	.0
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-12

AGE vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.3	.0
0-9	12.9	6.0	8.4	10.0	26.2	12.3
10-19	10.6	10.4	4.4	5.5	6.3	8.1
20-29	8.3	7.4	10.0	5.1	3.6	7.4
30-39	12.0	8.9	10.6	9.9	7.6	10.2
40-49	18.1	17.3	12.1	10.0	8.6	14.4
50-59	15.3	17.9	18.7	22.9	14.5	17.3
60-69	13.4	21.5	16.2	18.6	16.6	16.6
70-79	7.9	9.4	14.2	14.7	12.7	10.9
80-89	1.4	1.2	5.3	3.3	3.3	2.6
90 UP	.0	.0	.0	.0	.2	.0
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-13

SEX vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
MALE	40.8	28.6	20.9	47.2	45.1	35.2
FEMALE	59.2	71.4	79.1	52.8	54.9	64.8
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-14

SEX vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
MALE	51.0	46.9	43.7	52.1	52.3	49.2
FEMALE	49.0	53.1	56.3	47.9	47.6	50.8
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-15

SEX vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
MALE	49.2	47.5	48.3	47.6	49.8	48.6
FEMALE	50.8	52.5	51.7	52.4	50.2	51.4
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-16

YEAR vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	1.1	.2	.4	.3	.4	.5
1959	7.9	31.4	26.9	32.6	23.2	23.9
1960	17.8	26.7	27.0	29.4	25.0	24.7
1961	28.1	24.9	23.8	20.5	24.4	24.7
1962	45.1	16.9	21.9	17.3	27.0	26.1
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-17

YEAR vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	2.1	.7	1.0	1.0	1.5	1.4
1959	9.1	34.8	30.3	35.1	23.6	23.6
1960	19.6	28.3	28.2	31.5	25.1	25.1
1961	28.5	20.9	22.1	18.9	24.8	24.1
1962	40.7	15.3	18.4	13.5	25.1	25.8
TOTAL EE (IN THOUSANDS)	145.7	100.8	68.1	44.2	67.2	426.0

TABLE EE-18

YEAR vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	3.7	.2	2.2	.6	.9	2.0
1959	7.9	32.8	25.4	39.5	21.8	21.8
1960	18.5	32.6	24.1	26.5	28.3	24.6
1961	33.7	22.4	28.6	21.6	21.2	27.3
1962	36.2	12.0	19.7	11.7	27.8	24.3
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-19

INSTITUTION vs AGENT -- ESTIMATED EXPOSED (LOW)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
1	6.8	8.2	.0	10.7	1.1	5.6
2	1.6	.8	.9	.5	.7	1.0
3	1.6	6.1	3.2	.9	4.6	3.5
4	4.5	4.5	1.0	2.8	1.4	3.1
5	3.0	1.7	10.3	.9	2.7	3.6
6	4.0	6.4	.6	1.1	5.4	3.9
7	.5	.3	3.7	.9	1.6	1.3
8	10.6	9.3	.9	14.8	4.7	8.1
9	1.8	7.9	1.5	24.0	2.6	6.7
10	6.4	1.8	2.5	3.8	1.4	3.2
11	3.5	2.1	1.3	5.6	2.4	2.8
12	3.0	1.5	10.5	.1	.8	3.2
13	.5	.2	.4	.0	.4	.3
14	2.7	4.4	5.2	.0	9.6	4.4
15	2.4	3.7	6.6	3.7	4.8	4.1
16	.7	2.3	.8	.2	2.8	1.5
17	1.6	1.1	.5	5.5	2.4	1.9
18	.3	.6	.8	.8	.2	.5
19	2.6	1.5	2.5	.9	.8	1.7
20	1.4	2.6	16.8	6.6	8.5	6.4
21	10.2	5.6	9.9	2.2	13.5	8.2
22	5.9	2.1	5.9	1.6	3.0	3.8
23	1.0	1.7	3.7	.0	.3	1.4
24	.5	2.9	.1	.0	.4	1.0
25	1.4	.1	1.3	.2	1.1	.8
26	8.3	7.4	1.1	3.0	3.9	5.3
27	3.0	2.2	2.3	2.4	9.7	3.6
28	1.8	1.6	.0	1.1	.1	1.1
29	.8	.0	.3	.0	.3	.3
30	.3	.3	.1	.0	.6	.3
31	2.2	2.2	.8	2.6	2.0	2.0
32	3.6	.7	1.5	.0	2.4	1.7
33	1.2	6.2	.9	2.7	3.0	3.1
34	.2	.0	1.9	.1	1.1	.6
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-20

INSTITUTION vs AGENT -- ESTIMATED EXPOSED (MID)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
1	6.7	6.4	.0	.7	2.0	4.2
2	1.7	.9	1.4	.6	.9	1.2
3	.7	7.2	.9	.1	2.9	2.6
4	4.8	2.9	3.5	1.4	3.5	3.6
5	2.7	3.1	11.4	.7	2.3	3.9
6	3.3	5.0	.7	2.3	5.8	3.6
7	1.2	1.0	2.4	.4	1.7	1.3
8	15.6	5.5	.8	35.1	11.5	12.2
9	2.9	10.1	3.1	18.3	3.3	6.3
10	4.5	3.2	3.8	2.1	1.0	3.3
11	3.8	1.9	1.9	6.2	3.3	3.2
12	3.3	1.4	5.8	.4	1.8	2.7
13	1.1	.3	1.7	.3	2.7	1.2
14	1.8	1.7	4.8	.2	3.3	2.4
15	1.1	4.3	6.8	3.0	2.9	3.2
16	.6	4.6	.8	.2	3.9	2.1
17	1.1	1.3	.5	10.2	5.6	2.7
18	1.1	1.2	2.3	2.5	.7	1.4
19	3.0	4.2	1.3	.1	1.2	2.4
20	1.0	2.2	13.5	6.5	7.4	4.9
21	7.8	7.3	7.3	1.0	7.6	6.9
22	5.7	1.4	5.2	1.1	3.1	3.7
23	.8	1.8	1.3	.0	.4	1.0
24	1.1	6.1	.7	.3	.4	2.0
25	1.2	.5	1.5	.3	1.8	1.1
26	6.8	4.9	1.5	.7	1.9	4.1
27	4.0	2.0	3.9	1.2	2.4	2.9
28	.9	1.2	.0	.7	.0	.7
29	1.0	.1	.2	.0	.7	.5
30	.9	.5	.3	.0	.5	.5
31	1.4	1.0	2.4	.2	.3	1.2
32	2.9	1.1	1.4	.3	2.4	1.9
33	2.7	3.6	1.9	2.1	4.6	3.1
34	.7	.1	5.0	.6	5.9	2.1
TOTAL EE (IN THOUSANDS)	145.6	100.8	68.1	44.2	67.2	425.9

TABLE EE-21

INSTITUTION vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
1	4.2	2.0	.0	.9	.7	2.1
2	1.4	.5	2.2	.5	.6	1.2
3	.8	3.7	.3	.0	1.3	1.2
4	2.1	1.5	4.2	8.7	5.9	3.8
5	4.0	3.5	9.1	1.8	2.4	4.4
6	1.2	.9	.0	3.4	2.3	1.3
7	2.0	.8	1.4	1.2	3.0	1.7
8	20.2	6.4	2.6	34.4	16.4	15.5
9	6.7	5.9	1.6	15.6	4.0	6.3
10	6.3	5.3	8.3	3.5	2.1	5.5
11	3.0	1.8	4.6	4.6	5.2	3.6
12	3.3	.4	7.2	.0	1.4	2.8
13	1.0	.3	1.6	.2	2.8	1.2
14	.2	.0	3.3	.0	3.2	1.2
15	1.2	1.8	4.2	1.4	4.0	2.3
16	.9	9.3	2.3	.2	1.9	2.8
17	1.9	.6	.1	3.4	3.3	1.7
18	1.5	2.0	2.4	2.0	.6	1.7
19	2.7	5.6	2.1	.0	2.4	2.8
20	1.4	1.0	10.1	10.9	9.1	5.3
21	10.2	15.3	8.8	1.5	5.0	9.1
22	3.1	2.0	2.7	.7	2.9	2.5
23	.4	1.2	.5	.0	.4	.5
24	2.0	17.5	2.7	.3	.8	4.7
25	1.0	.7	2.3	.6	2.8	1.4
26	1.5	2.5	1.1	.0	.7	1.3
27	3.1	.2	4.1	.0	2.7	2.3
28	.4	.4	.0	.3	.1	.3
29	1.3	.3	.9	.0	1.3	.9
30	3.2	1.7	.6	.0	.4	1.6
31	.6	.0	2.0	.0	.1	.6
32	3.9	.4	1.5	.0	1.7	2.0
33	2.8	4.3	4.0	4.0	7.0	4.0
34	.0	.2	1.2	.0	1.2	.5
TOTAL EE (IN THOUSANDS)	21.7	11.6	11.7	7.6	9.1	61.6

TABLE EE-22

PERCENTAGE USAGE OF COMMON PRACTICES FOR EACH OF 34 INSTITUTIONS

INSTI-TUTION	COMMON PRACTICES H	NP	C	E	O	EE FOR INSTITUTION	EE AS PERCENT OF TOTAL
1	41.7	38.6	.2	14.4	5.1	39888	4.7
2	43.9	19.4	19.7	6.0	11.1	9536	1.1
3	10.6	57.0	11.1	2.0	19.2	24826	2.9
4	38.9	26.9	12.1	9.2	12.8	29227	3.4
5	22.8	16.2	48.0	2.7	10.2	32884	3.8
6	27.9	39.4	3.0	6.0	23.8	30259	3.5
7	23.6	12.4	37.6	6.2	20.2	11417	1.3
8	39.8	17.6	1.6	28.0	13.1	91224	10.7
9	13.1	35.0	6.0	38.5	7.3	55452	6.5
10	46.3	19.5	17.8	10.8	5.7	29227	3.4
11	35.4	16.4	10.3	22.6	15.4	26252	3.1
12	32.6	12.0	47.3	.9	7.2	25134	2.9
13	32.3	8.5	23.0	2.6	33.7	6889	.8
14	19.2	23.8	26.4	.5	30.1	27083	3.2
15	13.2	27.8	31.6	10.8	16.6	30271	3.5
16	11.3	51.1	8.7	1.4	27.5	16072	1.9
17	17.4	12.9	3.6	38.3	27.7	19759	2.3
18	24.0	23.0	26.9	18.9	7.2	8899	1.0
19	39.1	34.8	15.5	2.8	7.9	18325	2.1
20	6.2	10.7	45.8	14.7	22.5	47508	5.5
21	34.4	23.1	19.5	2.5	20.5	65149	7.6
22	45.4	12.1	25.1	4.2	13.2	31158	3.6
23	21.7	38.4	34.8	0	5.1	9774	1.1
24	16.2	73.3	5.6	1.2	3.7	15289	1.8
25	37.5	8.4	25.7	3.6	24.8	8445	1.0
26	46.2	34.4	5.0	4.9	9.5	37658	4.4
27	33.2	16.1	17.3	6.3	27.1	27257	3.2
28	43.1	41.8	.7	12.4	2.1	7061	.8
29	62.7	5.7	11.1	1.2	19.3	3916	.5
30	52.3	22.7	7.6	0	17.4	4406	.5
31	32.8	26.5	19.0	10.8	10.8	12488	1.5
32	53.3	11.8	13.9	1.1	19.9	15530	1.8
33	21.2	39.9	9.0	9.7	20.2	26822	3.1
34	11.3	1.9	42.7	2.8	41.4	11350	1.3
TOTAL	29.8	25.5	17.2	11.9	15.6	856435	

TABLE EE-23

OPERATION vs AGENT -- ESTIMATED EXPOSED (LOW)

PERCENT DISTRIBUTION WITHIN COMMON PRACTICE

	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
1	18.6	11.4	9.0	48.0	38.7	21.9
3	13.0	6.7	2.8	8.4	10.8	8.4
55	8.4	3.5	10.6	10.8	12.4	8.4
60	19.7	41.5	47.0	4.1	9.4	27.2
65	9.5	6.3	19.3	12.8	11.9	11.2
73	14.7	21.9	2.9	4.0	7.2	12.0
90	16.1	8.8	8.5	12.0	9.5	11.0
TOTAL EE (IN THOUSANDS)	86.6	105.1	67.3	50.0	57.3	366.3

TABLE EE-24

OPERATION vs AGENT -- ESTIMATED EXPOSED (MID)

PERCENT DISTRIBUTION WITHIN COMMON PRACTICE

	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
1	32.3	36.1	28.2	33.4	24.8	31.5
2	12.0	9.9	14.3	8.1	14.1	11.8
3	11.9	12.0	8.8	9.2	7.1	10.4
4	4.8	5.0	3.8	3.7	7.3	5.0
5	3.6	2.8	6.6	4.1	5.4	4.3
6	2.4	4.7	1.4	2.6	3.7	3.0
7	3.6	4.0	1.6	1.9	7.1	3.8
8	1.2	1.2	1.5	2.1	1.5	1.4
9	3.8	2.4	3.3	3.2	2.2	3.1
10	1.9	1.9	1.0	1.6	1.6	1.7
11	2.3	1.8	2.5	2.2	1.7	2.1
12	1.4	1.3	1.5	2.1	1.8	1.5
13	1.4	1.8	1.8	1.0	1.4	1.5
14	1.2	1.3	3.1	2.8	1.7	1.8
15	.4	.3	.7	1.1	1.1	.6
16	3.0	3.1	.6	.8	2.0	2.2
17	3.0	2.2	1.6	2.6	1.9	2.4
18	2.1	1.9	7.1	8.1	4.0	3.8
19	2.2	2.0	1.5	2.7	2.3	2.1
20	2.2	1.9	1.4	1.0	2.2	1.9
21	1.5	1.1	2.3	3.0	1.9	1.7
22	.4	.5	1.6	.8	.7	.7
23	.3	.2	.2	.2	.4	.3
24	.8	.6	2.8	1.7	1.5	1.3
25	.2	.1	.9	.1	.3	.3
TOTAL EE (IN THOUSANDS)	145.6	100.8	68.1	44.2	67.2	426.0

TABLE EE-25

OPERATION vs AGENT -- ESTIMATED EXPOSED (HIGH)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.0	.0	.0	.0	.0	.0
12	43.4	32.4	1.5	26.1	15.8	27.2
33	17.6	19.8	7.1	.0	19.1	14.1
44	19.2	22.6	46.6	37.2	36.3	29.8
48	19.8	25.3	44.8	36.7	28.9	29.0
TOTAL EE (IN THOUSANDS)	21.8	11.6	11.7	7.6	9.1	61.7

TABLE EE-26

OPERATION vs AGENT -- ESTIMATED EXPOSED (ALL)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
UNKNOWN	.1	.0	.0	.0	.1	.0
1	6.5	5.6	4.1	24.0	16.7	9.6
2	.9	.9	.0	.9	.6	.7
3	4.6	3.3	1.3	4.2	4.7	3.6
4	1.1	1.8	.2	1.2	.8	1.1
5	.6	.4	.0	.3	.3	.4
6	.9	1.0	.2	.5	.2	.7
7	.3	.3	.2	.5	.2	.3
8	.1	.0	.0	.3	.1	.1
9	.2	.1	.2	.0	.1	.2
10	1.9	1.1	1.2	1.7	1.9	1.5
12	3.8	1.8	.1	2.0	1.1	2.0
13	.5	.3	.0	.2	.4	.3
15	.3	.0	.0	.0	1.5	.4
16	1.6	1.4	.0	.3	2.8	1.3
17	.0	.1	.0	.1	.1	.0
20	1.3	1.1	.3	.9	2.7	1.2
21	.8	.8	.0	.3	.9	.6
22	.2	.0	.1	.0	.2	.1
23	.3	.3	.0	.3	.3	.2
25	.0	.0	.0	.2	.2	.1
26	.5	.2	.2	.3	.3	.3
27	1.8	1.0	.7	1.1	.9	1.2
28	.2	.1	.2	.2	.1	.2
30	3.2	3.7	3.0	1.0	1.1	2.7
31	.0	.0	.0	.0	.0	.0
32	1.0	.8	.6	.8	.4	.8
33	1.6	1.1	.6	.0	1.3	1.0
34	1.3	.9	.6	.4	1.1	.9
36	.6	.5	.2	.8	.5	.5
39	.1	.0	.2	.1	.1	.1
40	1.6	1.1	2.9	1.7	1.1	1.6
41	.8	.6	1.0	.7	.6	.7
42	.7	.6	1.4	1.3	.9	.9
43	.0	.0	.0	.0	.0	.0
44	1.7	1.2	3.7	2.8	2.5	2.2
45	1.2	.9	3.3	3.6	2.0	1.9
46	.1	.0	.3	.0	.1	.1
47	.5	.3	1.3	.8	.8	.6
48	1.8	1.4	3.6	2.8	2.0	2.1
50	1.9	1.1	3.5	1.3	1.4	1.8
51	.3	.1	.3	.5	.5	.3
52	.1	.0	.4	.0	.2	.1
54	.9	1.1	.8	.6	.9	.9
55	3.0	1.7	4.9	5.4	5.4	3.6
56	.0	.0	.0	.0	.0	.0
57	.9	.5	1.0	1.3	.9	.9
58	.4	.4	.3	.3	.4	.4
59	.3	.3	.7	.3	.4	.4

TABLE EE-26 (Cont'd)

OPERATION vs AGENT -- ESTIMATED EXPOSED (ALL)

	PERCENT DISTRIBUTION WITHIN COMMON PRACTICE					
	H	NP	C	E	O	ALL
60	6.9	20.5	21.5	2.1	4.1	11.9
62	.0	.3	.9	.0	.3	.3
63	.0	.0	.3	.0	.0	.0
65	3.3	3.1	8.8	6.4	5.1	4.9
66	.9	1.0	3.2	1.4	1.0	1.4
67	.0	.0	.0	.0	.0	.0
68	.3	.4	.8	.5	.4	.4
70	1.3	2.2	.6	1.1	1.8	1.5
71	1.1	1.1	1.4	1.9	1.0	1.2
72	.2	.2	.0	.0	.1	.1
73	5.2	10.8	1.3	2.0	3.1	5.2
75	1.5	.8	1.4	1.2	.9	1.2
76	.6	.5	.7	.6	.8	.6
77	.6	.5	.5	.8	.6	.6
80	1.8	1.4	.6	.3	.6	1.1
81	2.9	1.6	1.5	1.4	2.1	2.0
84	3.8	2.5	1.0	1.8	1.9	2.4
85	1.9	1.0	.8	.7	1.1	1.2
86	1.8	1.4	.3	.4	1.0	1.1
87	.4	.3	.4	.2	.2	.3
88	.8	.9	.8	.5	.7	.8
89	.8	.8	1.0	2.0	.8	1.0
90	5.7	4.3	3.9	6.0	4.1	4.8
92	2.5	2.1	1.7	1.0	4.2	2.3
93	.7	.5	.5	.8	.8	.6
95	1.3	1.0	1.4	.5	.7	1.1
98	.8	.4	.0	.2	.2	.4
99	.0	.0	.0	.0	.0	.0
TOTAL EE (IN THOUSANDS)	245.9	213.0	147.2	100.0	132.6	838.7

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TABLE DR-1

PREVIOUS OPERATION vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
NO PREVIOUS OP	.00210	.00162	.00211	.00117	.00194	.00181
NO HALOTHANE	.00913	.00742	.00873	.00296	.01340	.00825
HAD HALOTHANE	.00713	.00559	.00991	.00000	.01830	.00841
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00258	.00201	.00263	.00123	.00293	.00230
STANDARD (RATIO)	1.12421	.87474	1.14594	.53562	1.27422	
INDIRECT M.R.	1.08807	.88490	1.14219	.57205	1.25955	

TABLE DR-2

PREVIOUS OPERATION vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
NO PREVIOUS OP	.01518	.01519	.02862	.01671	.02697	.01931
NO HALOTHANE	.03784	.03416	.08156	.03780	.04448	.04606
HAD HALOTHANE	.03455	.04289	.10270	.02123	.04972	.04314
OVER-ALL	.01727	.01709	.03401	.01854	.02988	.02207
STANDARDIZED DEATH RATE	.01750	.01745	.03483	.01849	.02898	.02207
STANDARD (RATIO)	.79275	.79055	1.57806	.83768	1.31295	
INDIRECT M.R.	.78731	.77943	1.58125	.84619	1.28431	

TABLE DR-3

PREVIOUS OPERATION vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
NO PREVIOUS OP	.08201	.09486	.08784	.05854	.10831	.08678
NO HALOTHANE	.12606	.14971	.14676	.07058	.18151	.13541
HAD HALOTHANE	.10249	.17416	.27333	.08491	.11618	.11834
OVER-ALL	.08661	.10261	.09798	.06076	.11715	.09335
STANDARDIZED DEATH RATE	.08763	.10401	.10168	.06091	.11661	.09335
STANDARD (RATIO)	.93880	1.11427	1.08928	.65251	1.24920	
INDIRECT M.R.	.92943	1.11439	1.05155	.61601	1.28239	

TABLE DR-4

PHYSICAL STATUS vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	.00365	.00150	.00356	.00104	.00321	.00257
RISK 1	.00045	.00038	.00034	.00026	.00034	.00036
RISK 2	.00308	.00331	.00316	.00272	.00320	.00315
RISK 3	.01968	.01788	.02128	.01548	.02179	.01924
RISK 4	.04192	.03158	.03543	.08000	.23171	.05650
RISK 5	.00116	.00115	.00126	.00778	.00623	.00183
RISK 6	.03360	.02508	.02647	.04348	.06571	.03351
RISK 7	.53333	.09722	.16923	.08000	.54167	.20398
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00264	.00192	.00235	.00210	.00349	.00230
STANDARD (RATIO)	1.14933	.83521	1.02436	.91190	1.51715	
INDIRECT M.R.	1.08144	.83644	.96755	.73254	1.47004	

TABLE DR-5

PHYSICAL STATUS vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	.01778	.01507	.02927	.01896	.02328	.01991
RISK 1	.00192	.00172	.00335	.00256	.00356	.00238
RISK 2	.01517	.01600	.02555	.01476	.02116	.01775
RISK 3	.06917	.06922	.10561	.05521	.06916	.07241
RISK 4	.15543	.15395	.18664	.22426	.18445	.17272
RISK 5	.01123	.01231	.01358	.02075	.02326	.01444
RISK 6	.10898	.12158	.12488	.14422	.14384	.12531
RISK 7	.25232	.23720	.33753	.28507	.38659	.31475
OVER-ALL	.01727	.01709	.03401	.01855	.02988	.02207
STANDARDIZED DEATH RATE	.01943	.01941	.02855	.02119	.02532	.02207
STANDARD (RATIO)	.88013	.87930	1.29332	.96003	1.14707	
INDIRECT M.R.	.87097	.87120	1.22261	.91890	1.15360	

TABLE DR-6

PHYSICAL STATUS vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	.11369	.08682	.08147	.06148	.09957	.09642
RISK 1	.02454	.02452	.01634	.01355	.03358	.02243
RISK 2	.05471	.06893	.04941	.03812	.05859	.05470
RISK 3	.12471	.16599	.18187	.11453	.15306	.14605
RISK 4	.15892	.23140	.18582	.17919	.35531	.20587
RISK 5	.04665	.06759	.05725	.04898	.07606	.05699
RISK 6	.22143	.12996	.17615	.16008	.17741	.17439
RISK 7	.44164	.43689	.36689	.62121	.43348	.42410
OVER-ALL	.08663	.10263	.09800	.06080	.11720	.09337
STANDARDIZED DEATH RATE	.09467	.09832	.09254	.07787	.10494	.09337
STANDARD (RATIO)	1.01393	1.05300	.99112	.83396	1.12387	
INDIRECT M.R.	.98819	1.07250	.96583	.77747	1.11162	

TABLE DR-7

LENGTH vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	.01333	.00735	.00000	.00000	.02913	.01144
1-28 MIN	.00069	.00075	.00078	.00043	.00164	.00081
29-58	.00153	.00164	.00130	.00021	.00145	.00132
59-118	.00309	.00306	.00448	.00121	.00292	.00293
119-238	.00501	.00438	.00413	.00365	.00517	.00452
239-388	.01053	.00639	.01772	.00360	.01327	.01009
389 UP	.02286	.02299	.02083	.03846	.01005	.02077
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00247	.00235	.00275	.00114	.00268	.00230
STANDARD (RATIO)	1.07589	1.02224	1.19433	.49523	1.15420	
INDIRECT M.R.	1.07798	1.03635	1.15552	.48846	1.12542	

TABLE DR-8

LENGTH vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	.01606	.05714	.26190	.02128	.02331	.02722
1-28 MIN	.00390	.00481	.01157	.00673	.00748	.00609
29-58	.00586	.00567	.01341	.00607	.01515	.00831
59-118	.01077	.01215	.02421	.01254	.02252	.01551
119-238	.02137	.02309	.04307	.01875	.03923	.02734
239-388	.04150	.03333	.07729	.03788	.05880	.04697
389 UP	.09914	.11883	.13291	.07024	.11555	.10701
OVER-ALL	.01727	.01709	.03401	.01855	.02988	.02207
STANDARDIZED DEATH RATE	.01736	.01809	.03551	.01648	.03069	.02207
STANDARD (RATIO)	.78658	.81973	1.60864	.74681	1.39039	
INDIRECT M.R.	.77941	.80157	1.59893	.72854	1.38169	

TABLE DR-9

LENGTH vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	.09859	.13333	.07692	1.00000	.10000	.10769
1-28 MIN	.03590	.07692	.09589	1.00000	.05263	.05669
29-58	.08317	.03785	.08786	.04972	.15931	.08142
59-118	.05023	.08897	.10067	.05455	.12720	.08029
119-238	.07209	.07614	.08536	.05708	.09442	.07742
239-388	.10603	.10439	.10394	.06064	.12052	.10332
389 UP	.14126	.18362	.26866	.21990	.23636	.17373
OVER-ALL	.08662	.10262	.09799	.06078	.11717	.09336
STANDARDIZED DEATH RATE	.08237	.09440	.11011	.07978	.12364	.09336
STANDARD (RATIO)	.88232	1.01108	1.17938	.85455	1.32432	
INDIRECT M.R.	.87587	1.01109	1.17219	.68932	1.35117	

TABLE DR-10

AGE vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	.01316	0/0	.00000	0/0	.00000	.00385
0-9	.00178	.00110	.00208	.00069	.00093	.00114
10-19	.00107	.00073	.00103	.00000	.00096	.00076
20-29	.00139	.00071	.00080	.00150	.00271	.00108
30-39	.00123	.00035	.00111	.00118	.00160	.00089
40-49	.00176	.00100	.00133	.00226	.00215	.00145
50-59	.00314	.00245	.00290	.00324	.00887	.00339
60-69	.00487	.00411	.00748	.00407	.01048	.00541
70-79	.01341	.00856	.01846	.00730	.01329	.01165
80-89	.03448	.01797	.08190	.00741	.03623	.02818
90 UP	.01351	.13462	.11111	0/0	.03030	.05000
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00264	.00175	.00333	.00192	.00381	.00230
STANDARD (RATIO)	1.14677	.76067	1.45030	.83438	1.65565	
INDIRECT M.R.	1.10858	.71451	1.27633	.71484	1.41535	

TABLE DR-11

AGE vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	.01613	.12500	.00000	.00000	.01408	.01230
0-9	.02050	.01427	.03966	.02054	.02426	.02332
10-19	.00334	.00366	.00752	.00282	.00802	.00462
20-29	.00586	.00458	.00613	.00265	.01146	.00594
30-39	.00716	.00596	.01023	.00474	.00894	.00746
40-49	.01087	.01015	.02038	.00601	.01820	.01266
50-59	.01769	.01828	.03892	.01820	.03022	.02296
60-69	.02688	.02773	.05434	.03092	.04271	.03451
70-79	.05135	.04938	.10367	.05972	.07734	.06495
80-89	.10732	.07429	.13260	.14017	.15274	.11416
90 UP	.26804	.41429	.18354	.07500	.33945	.26160
OVER-ALL	.01727	.01709	.03401	.01855	.02988	.02207
STANDARDIZED DEATH RATE	.01831	.01701	.03405	.01838	.02820	.02207
STANDARD (RATIO)	.82961	.77076	1.54251	.83255	1.27759	
INDIRECT M.R.	.82036	.76624	1.53528	.82643	1.26605	

TABLE DR-12

AGE vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	.00000	0/0	.00000	0/0	.00000	.00000
0-9	.08309	.14020	.14645	.08785	.09681	.10186
10-19	.05979	.07875	.05839	.02093	.09479	.06529
20-29	.06298	.10685	.03239	.04000	.11260	.06601
30-39	.08104	.13260	.04637	.02461	.09766	.07891
40-49	.08579	.11077	.08382	.06863	.13925	.09473
50-59	.11013	.10814	.08256	.04334	.12608	.09587
60-69	.09693	.06572	.13462	.07218	.11183	.09576
70-79	.08555	.11093	.12808	.07749	.13479	.10775
80-89	.13928	.19101	.13250	.11744	.20833	.15216
90 UP	.41667	1.00000	.57895	1.00000	.33333	.50000
OVER-ALL	.08663	.10262	.09802	.06079	.11718	.09337
STANDARDIZED DEATH RATE	.08907	.10887	.09704	.06010	.11906	.09337
STANDARD (RATIO)	.95397	1.16603	1.03924	.64369	1.27517	
INDIRECT M.R.	.94874	1.14026	1.02764	.61434	1.22769	

TABLE DR-13

SEX vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	.04000	0/0	.00000	.00000	.00000	.02083
MALE	.00313	.00308	.00487	.00097	.00312	.00292
FEMALE	.00237	.00154	.00199	.00151	.00260	.00196
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00265	.00209	.00300	.00132	.00279	.00230
STANDARD (RATIO)	1.15133	.90845	1.30611	.57551	1.21165	
INDIRECT M.R.	1.14473	.88841	1.19965	.52053	1.18607	

TABLE DR-14

SEX vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	.00000	0/0	0/0	0/0	.03571	.03030
MALE	.02091	.02120	.04620	.02176	.03478	.02708
FEMALE	.01345	.01343	.02432	.01501	.02444	.01717
OVER-ALL	.01727	.01709	.03401	.01854	.02988	.02207
STANDARDIZED DEATH RATE	.01714	.01727	.03513	.01835	.02955	.02207
STANDARD (RATIO)	.77642	.78259	1.59187	.83150	1.33883	
INDIRECT M.R.	.77213	.77857	1.59996	.82606	1.34500	

TABLE DR-15

SEX vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
MALE	.10001	.11012	.11022	.06900	.12650	.10431
FEMALE	.07325	.09570	.08625	.05318	.10767	.08274
OVER-ALL	.08661	.10261	.09798	.06077	.11715	.09335
STANDARDIZED DEATH RATE	.08641	.10279	.09804	.06096	.11693	.09335
STANDARD (RATIO)	.92571	1.10118	1.05026	.65306	1.25265	
INDIRECT M.R.	.91958	1.11364	1.05587	.63010	1.28482	

TABLE DR-16

YEAR vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	.00000	.00000	.00000	.00000	.00000	.00000
1959	.00378	.00230	.00204	.00110	.00263	.00219
1960	.00233	.00221	.00329	.00116	.00279	.00237
1961	.00320	.00164	.00224	.00176	.00371	.00250
1962	.00240	.00157	.00284	.00116	.00232	.00219
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00290	.00191	.00260	.00129	.00284	.00230
STANDARD (RATIO)	1.26136	.83176	1.13028	.55971	1.23621	
INDIRECT M.R.	1.18112	.85875	1.12689	.54700	1.23449	

TABLE DR-17

YEAR vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	.00000	.00000	.00000	.00000	.00000	.00000
1959	.01681	.01721	.03085	.01924	.03196	.02265
1960	.01666	.01577	.03565	.01596	.03153	.02216
1961	.01963	.01835	.03652	.02063	.02999	.02365
1962	.01688	.01830	.03542	.02112	.02783	.02113
OVER-ALL	.01727	.01709	.03401	.01854	.02988	.02207
STANDARDIZED DEATH RATE	.01724	.01717	.03419	.01898	.02988	.02207
STANDARD (RATIO)	.78121	.77808	1.54914	.85985	1.35381	
INDIRECT M.R.	.78995	.76117	1.54840	.82974	1.36460	

TABLE DR-18

YEAR vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	.00000	.00000	.00000	.00000	.00000	.00000
1959	.10131	.10342	.11324	.05768	.12919	.09950
1960	.10303	.09227	.11293	.06704	.12004	.10059
1961	.08112	.09871	.07147	.05677	.13567	.08627
1962	.08799	.13583	.10667	.06716	.09310	.09520
OVER-ALL	.08662	.10261	.09798	.06079	.11716	.09336
STANDARDIZED DEATH RATE	.09121	.10541	.09822	.06103	.11758	.09336
STANDARD (RATIO)	.97706	1.12907	1.05213	.65370	1.25946	
INDIRECT M.R.	.95480	1.07415	1.05757	.60992	1.26433	

TABLE DR-19

INSTITUTION vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.00119	.00035	.01515	.00000	.00482	.00068
2	.00910	.01044	.01085	.00000	.01571	.00980
3	.00000	.00124	.00047	.00234	.00114	.00100
4	.00155	.00084	.00436	.00215	.00738	.00191
5	.00424	.00762	.00302	.00216	.00717	.00433
6	.00029	.00178	.00686	.00557	.00032	.00141
7	.00837	.00940	.00281	.00221	.00987	.00516
8	.00142	.00051	.00168	.00149	.00186	.00118
9	.00187	.00204	.00495	.00117	.00341	.00180
10	.00357	.00484	.00885	.00156	.00384	.00422
11	.00330	.00322	.00796	.00287	.00581	.00390
12	.00651	.00381	.00071	.00000	.01499	.00297
13	.00924	.00000	.00830	.00000	.00000	.00513
14	.00211	.00065	.00172	.00000	.00090	.00119
15	.00237	.00285	.00113	.00000	.00254	.00187
16	.00462	.00162	.00177	.00000	.00251	.00222
17	.00142	.00000	.00290	.00109	.00293	.00142
18	.01261	.00000	.00576	.00246	.04724	.00676
19	.00539	.00391	.00419	.00000	.00895	.00459
20	.00169	.00221	.00053	.00211	.00227	.00137
21	.00136	.00051	.00090	.00184	.00039	.00086
22	.00271	.00277	.00226	.00000	.00115	.00224
23	.00000	.00169	.00121	0/0	.00000	.00114
24	.01656	.00690	.08333	.00000	.04206	.01165
25	.01144	.01266	.01764	.00000	.01713	.01410
26	.00140	.00141	.00538	.00000	.00221	.00154
27	.00307	.00127	.00508	.00000	.00072	.00173
28	.00063	.00058	.00000	.00000	.00000	.00051
29	.00742	.02632	.00565	.03704	.01031	.00901
30	.01379	.01038	.02062	0/0	.00804	.01144
31	.00211	.00214	.00938	.00000	.00351	.00250
32	.00255	.00143	.00499	.00000	.00148	.00257
33	.00382	.00336	.00158	.00291	.00176	.00301
34	.00575	.00000	.00076	.00000	.01061	.00399
OVER-ALL	.00270	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00269	.00233	.00494	.00137	.00409	.00230
STANDARD (RATIO)	1.16799	1.01519	2.15054	.59642	1.77922	
INDIRECT M.R.	1.09606	.90688	.98075	.63944	1.32422	

TABLE DR-20

INSTITUTION vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.01247	.00460	.13514	.00915	.01765	.01022
2	.06195	.06720	.11907	.05479	.09841	.07812
3	.01194	.00843	.02483	.00000	.01549	.01089
4	.00898	.02198	.06240	.06056	.04888	.02862
5	.04534	.05396	.02745	.09668	.06346	.04151
6	.01185	.01300	.02954	.03494	.01113	.01417
7	.04189	.03216	.03736	.17561	.08657	.05263
8	.01301	.01058	.04044	.01166	.00869	.01199
9	.02527	.01488	.03089	.01605	.02481	.01898
10	.02019	.02966	.06577	.03163	.07588	.03460
11	.01053	.01343	.02846	.02681	.04236	.02115
12	.01990	.00919	.02692	.01765	.05513	.02485
13	.02072	.01813	.05281	.01613	.02392	.02918
14	.00631	.00283	.01235	.03030	.01026	.00879
15	.02260	.01513	.02695	.02861	.04760	.02587
16	.03186	.02857	.07083	.03093	.03106	.03244
17	.01517	.00297	.02550	.00243	.01482	.00905
18	.02349	.02617	.05105	.00534	.06098	.03120
19	.02185	.00964	.05945	.02941	.04321	.02198
20	.01870	.01431	.01802	.02146	.02993	.02104
21	.01128	.01405	.02186	.02772	.01927	.01546
22	.01811	.03094	.02472	.01266	.04186	.02379
23	.00762	.01292	.01029	0/0	.02062	.01141
24	.04970	.02629	.19089	.14815	.18261	.04881
25	.04701	.07227	.09498	.12422	.11029	.08029
26	.00828	.01569	.05138	.01534	.01800	.01376
27	.00552	.00853	.02194	.01119	.01585	.01111
28	.00506	.00169	.00000	.00662	.03226	.00440
29	.02033	.04459	.08284	.00000	.02876	.02797
30	.03630	.03592	.05978	0/0	.03073	.03717
31	.01431	.01331	.02939	.01449	.05069	.02069
32	.01393	.00647	.03529	.00000	.02228	.01702
33	.02674	.01512	.05460	.04016	.03065	.02833
34	.00824	.02222	.01567	.01852	.01527	.01477
OVER-ALL	.01727	.01709	.03401	.01855	.02989	.02208
STANDARDIZED DEATH RATE	.01879	.01790	.04441	.02994	.03488	.02208
STANDARD (RATIO)	.85119	.81091	2.01162	1.35627	1.58020	
INDIRECT M.R.	.79612	.75740	1.31702	1.05388	1.40541	

TABLE DR-21

INSTITUTION vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.06076	.08800	1.00000	.02985	.14474	.06960
2	.14169	.21795	.12759	.11628	.28378	.15493
3	.06186	.07792	.09091	0/0	.10370	.07904
4	.07186	.14070	.11252	.06901	.11221	.09466
5	.13074	.15528	.08927	.13924	.26441	.13213
6	.11150	.19048	1.00000	.05904	.06849	.10231
7	.13725	.09091	.14595	.18919	.21221	.16013
8	.07544	.06289	.08589	.03867	.08528	.06660
9	.09193	.11039	.21212	.06969	.10099	.09595
10	.05080	.06748	.09311	.02909	.10599	.06785
11	.07950	.14516	.06713	.09254	.08721	.08690
12	.08021	.21154	.06480	1.00000	.22360	.09072
13	.13333	.16667	.14414	.00000	.06545	.11250
14	.11111	1.00000	.02284	1.00000	.03987	.04244
15	.08156	.19767	.10364	.17600	.09476	.11819
16	.14103	.09572	.12378	.00000	.12935	.10843
17	.05760	.05797	.36000	.01504	.08669	.06267
18	.08989	.15985	.11285	.01911	.13846	.10549
19	.16597	.04889	.11957	0/0	.15326	.11664
20	.04268	.02479	.05600	.06877	.11087	.07141
21	.04586	.04169	.06210	.04202	.13800	.05572
22	.10106	.15217	.11364	.03704	.13043	.11483
23	.09000	.08387	.10294	0/0	.00000	.07989
24	.11359	.13939	.26037	.21875	.37398	.16015
25	.10843	.11957	.14148	.06383	.17105	.13659
26	.09065	.12689	.13514	1.00000	.23810	.12921
27	.07798	.29412	.08539	0/0	.07308	.08441
28	.02439	.04167	0/0	.00000	.00000	.02367
29	.15497	.15909	.16529	1.00000	.11364	.15000
30	.09834	.11312	.16250	0/0	.11364	.10638
31	.15432	.31250	.09843	0/0	.21429	.13004
32	.07476	.10526	.12981	0/0	.10920	.08884
33	.13734	.11011	.05859	.05937	.08696	.09608
34	.04762	.09091	.12270	0/0	.12500	.11677
OVER-ALL	.08668	.10273	.09808	.06084	.11734	.09345
STANDARDIZED DEATH RATE	.08845	.11781	.14317	.13107	.13645	.09345
STANDARD (RATIO)	.94644	1.26061	1.53207	1.40255	1.46008	
INDIRECT M.R.	.95621	.98878	1.01135	.71600	1.31755	

TABLE DR-22

INSTITUTION vs AGENT -- DEATH RATES (ALL)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.01124	.00356	.06731	.00087	.01846	.00732
2	.05125	.04845	.08622	.03723	.08218	.06049
3	.00938	.00743	.00719	.00205	.01016	.00803
4	.00914	.01232	.05912	.03374	.04997	.02394
5	.04244	.04766	.02144	.05771	.05530	.03512
6	.01056	.00857	.02508	.02995	.00826	.01085
7	.05331	.03091	.02232	.07542	.07581	.04532
8	.01814	.00712	.03474	.01159	.01745	.01456
9	.03466	.01300	.03499	.01089	.02469	.01730
10	.01659	.02598	.05357	.01319	.04718	.02661
11	.01359	.01627	.03004	.02019	.03586	.02070
12	.02129	.00986	.01434	.02954	.05992	.01966
13	.03095	.02017	.05826	.01111	.02643	.03448
14	.00535	.00171	.00778	.04000	.00488	.00518
15	.01576	.01510	.01950	.01831	.02742	.01899
16	.03556	.02989	.05469	.01299	.02539	.03128
17	.01488	.00312	.02624	.00237	.01599	.00933
18	.03299	.03529	.04930	.00592	.06569	.03544
19	.03087	.01238	.03307	.00391	.05201	.02584
20	.01436	.00801	.01113	.01836	.02433	.01507
21	.01096	.01212	.01438	.01194	.01307	.01236
22	.01688	.02382	.01732	.00612	.03135	.01933
23	.00842	.01055	.00555	0/0	.01188	.00842
24	.05591	.04388	.21009	.13043	.17277	.06340
25	.03830	.06553	.07109	.07034	.09229	.06406
26	.00713	.01000	.04012	.00542	.01326	.01030
27	.01073	.00679	.02337	.00349	.00658	.01074
28	.00328	.00169	.00000	.00228	.01342	.00268
29	.03500	.06250	.07463	.04000	.03822	.04184
30	.05341	.04498	.07182	0/0	.02538	.04817
31	.01419	.00691	.03218	.00074	.01312	.01421
32	.01628	.00761	.03048	.00000	.01808	.01746
33	.03567	.01292	.04208	.02361	.02897	.02476
34	.00854	.02283	.01525	.01558	.01756	.01561
OVER-ALL	.01872	.01486	.02543	.01350	.02506	.01928
STANDARDIZED DEATH RATE	.01986	.01524	.03458	.01949	.02988	.01928
STANDARD (RATIO)	1.02997	.79004	1.79313	1.01086	1.54955	
INDIRECT M.R.	.96998	.75605	1.19044	.79763	1.38191	

TABLE DR-23

OPERATION vs AGENT -- DEATH RATES (LOW)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.00099	.00067	.00166	.00029	.00054	.00066
3	.00097	.00099	.00215	.00000	.00000	.00072
55	.00327	.00355	.00571	.00260	.00364	.00384
60	.00088	.00092	.00082	.00097	.00130	.00090
65	.00171	.00226	.00262	.00328	.00408	.00272
73	.00368	.00342	.00458	.00249	.00700	.00384
90	.00760	.00508	.00882	.00234	.01104	.00689
OVER-ALL	.00269	.00198	.00259	.00126	.00284	.00230
STANDARDIZED DEATH RATE	.00228	.00200	.00306	.00147	.00329	.00230
STANDARD (RATIO)	.99395	.87012	1.33105	.63878	1.43286	
INDIRECT M.R.	1.01449	.88122	1.21383	.58257	1.31601	

TABLE DR-24

OPERATION vs AGENT -- DEATH RATES (MID)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
1	.00178	.00219	.00311	.00250	.00317	.00233
2	.00372	.00488	.00746	.00583	.00701	.00545
3	.00719	.00615	.00829	.00538	.01099	.00730
4	.00957	.00970	.01685	.01033	.00945	.01052
5	.00841	.01035	.01181	.01139	.01860	.01192
6	.01781	.01280	.02152	.01135	.02579	.01726
7	.01996	.02006	.03526	.01675	.01959	.02075
8	.02089	.02088	.03507	.01178	.04175	.02552
9	.02325	.02952	.03139	.01205	.03959	.02653
10	.02488	.02617	.05063	.04313	.03053	.03046
11	.02514	.03636	.04815	.03153	.04136	.03469
12	.03733	.03214	.05652	.02784	.03221	.03709
13	.01889	.01965	.08252	.04651	.07436	.04209
14	.04028	.03304	.05047	.03615	.05137	.04291
15	.04018	.09122	.04839	.02800	.03624	.04393
16	.03499	.04531	.07565	.05181	.07232	.04607
17	.03566	.05193	.06452	.03422	.07207	.04688
18	.04191	.05586	.06254	.02644	.05333	.04841
19	.08156	.06462	.11581	.05063	.10599	.08225
20	.07644	.07207	.13180	.10526	.11945	.09214
21	.06762	.09983	.13604	.05659	.13600	.09776
22	.10511	.08347	.10280	.08719	.10657	.09887
23	.09627	.06989	.17910	.04651	.16573	.12033
24	.10378	.13146	.14020	.09953	.11292	.12107
25	.11340	.14894	.13656	.21519	.13693	.13747
OVER-ALL	.01727	.01709	.03401	.01855	.02988	.02207
STANDARDIZED DEATH RATE	.01857	.02080	.03004	.01819	.02793	.02207
STANDARD (RATIO)	.84126	.94218	1.36097	.82400	1.26533	
INDIRECT M.R.	.82815	.90605	1.32020	.74133	1.25693	

TABLE DR-25

OPERATION vs AGENT -- DEATH RATES (HIGH)

	H	NP	C	E	O	ALL
UNKNOWN	0/0	0/0	0/0	0/0	0/0	0/0
12	.09162	.09742	.12371	.06538	.18462	.09902
33	.14068	.19416	.16867	1.00000	.14342	.16012
44	.06212	.07901	.11504	.06548	.10240	.08852
48	.04601	.04663	.06579	.04679	.07578	.05653
OVER-ALL	.08662	.10262	.09798	.06077	.11715	.09335
STANDARDIZED DEATH RATE	.07763	.09251	.11184	.20216	.12370	.09335
STANDARD (RATIO)	.83155	.99096	1.19798	2.16552	1.32504	
INDIRECT M.R.	.84865	1.03609	1.24483	.74537	1.24911	

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TABLE DR-26

OPERATION vs AGENT -- DEATH RATES (ALL)

	H	NP	C	E	O	ALL
UNKNOWN	.02273	.05882	.03846	.11364	.03109	.03818
1	.00099	.00067	.00166	.00029	.00054	.00066
2	.00277	.00164	.00990	.00215	.00131	.00224
3	.00097	.00099	.00215	.00000	.00000	.00072
4	.00110	.00131	.00000	.00168	.00284	.00143
5	.02520	.03317	.03390	.05788	.02180	.03047
6	.00174	.00246	.01111	.00187	.00403	.00274
7	.00375	.00000	.01351	.00435	.00386	.00422
8	.00366	.00495	.00000	.00000	.00000	.00181
9	.01972	.01320	.00743	.04255	.01282	.01560
10	.00188	.00392	.00346	.00422	.00446	.00324
12	.09162	.09742	.12371	.06538	.18462	.09902
13	.06551	.08537	.01786	.03382	.10201	.07419
15	.00727	.02538	.00000	.00000	.01329	.01209
16	.02068	.02319	.06494	.01873	.01987	.02133
17	.18009	.05882	.08333	.03906	.04908	.08629
20	.01012	.01137	.04183	.00887	.00888	.01138
21	.00797	.00355	.02985	.00909	.00632	.00679
22	.09627	.06989	.17910	.04651	.16573	.12033
23	.01662	.00722	.00000	.00000	.01053	.01017
25	.01778	.01914	.05797	.03030	.03846	.02854
26	.02864	.04833	.06250	.02147	.04076	.03608
27	.03566	.05193	.06452	.03422	.07207	.04688
28	.03604	.03860	.03245	.03590	.08054	.04037
30	.00101	.00076	.00114	.00289	.00068	.00101
31	.00000	.00000	.00000	.00000	.00000	.00000
32	.00319	.00226	.00000	.00242	.00733	.00276
33	.14068	.19416	.16867	1.00000	.14342	.16012
34	.07644	.07207	.13180	.10526	.11945	.09214
36	.09299	.04944	.16787	.05495	.11303	.08611
39	.01393	.02069	.03143	.02830	.03175	.02437
40	.00722	.00876	.01212	.01106	.02633	.01155
41	.02288	.03156	.04595	.03628	.04162	.03409
42	.04028	.03304	.05047	.03615	.05137	.04291
43	.07407	1.00000	.11111	.00000	.24000	.08920
44	.06212	.07901	.11504	.06548	.10240	.08852
45	.04191	.05586	.06254	.02644	.05333	.04841
46	.04098	.08287	.09158	.18421	.12183	.08358
47	.10378	.13146	.14020	.09953	.11292	.12107
48	.04601	.04663	.06579	.04679	.07578	.05653
50	.00324	.00297	.00601	.01027	.00908	.00543
51	.04018	.09122	.04839	.02800	.03624	.04393
52	.11340	.14894	.13656	.21519	.13693	.13747
54	.00172	.00215	.00337	.00524	.00336	.00263
55	.00327	.00355	.00571	.00260	.00364	.00384
56	.00971	.00000	.12000	.00000	.02000	.01862
57	.06846	.09949	.13727	.05077	.14030	.09788
58	.02601	.02162	.05354	.03409	.03373	.03104
59	.10511	.08347	.10280	.08719	.10657	.09887
60	.00088	.00092	.00082	.00097	.00130	.00090
62	.00800	.00168	.00512	.00000	.00257	.00402

TABLE DR-26 (Cont'd)

OPERATION vs AGENT -- DEATH RATES (ALL)

	H	NP	C	E	O	ALL
63	.00000	.00000	.00518	.00000	.00000	.00249
65	.00171	.00226	.00262	.00328	.00408	.00272
66	.00563	.00457	.00667	.00488	.01159	.00641
67	.04902	.16667	.08108	.27778	.07843	.09541
68	.00250	.00524	.00177	.00000	.00361	.00268
70	.01832	.01287	.01895	.01156	.02604	.01722
71	.00144	.00451	.00720	.00053	.00152	.00315
72	.00000	.00211	.00000	.00000	.00000	.00082
73	.00368	.00342	.00458	.00249	.00700	.00384
75	.02257	.02410	.03305	.01088	.04043	.02599
76	.01799	.01170	.03304	.01585	.02041	.01988
77	.02268	.02091	.03693	.00966	.04405	.02580
80	.00669	.00869	.01278	.01176	.01826	.00917
81	.00126	.00118	.00181	.00143	.00179	.00142
84	.00268	.00381	.00470	.00708	.00619	.00396
85	.00377	.00691	.00650	.00280	.00392	.00470
86	.03499	.04531	.07565	.05181	.07232	.04607
87	.00398	.00543	.00781	.00000	.00441	.00503
88	.01889	.01965	.08252	.04651	.07436	.04209
89	.00000	.00118	.00198	.00049	.00177	.00097
90	.00760	.00508	.00882	.00234	.01104	.00689
92	.00398	.00545	.01018	.00400	.00742	.00606
93	.03768	.03039	.06737	.02584	.02582	.03627
95	.00761	.00849	.01093	.01887	.01114	.00958
98	.02451	.04135	.00685	.01860	.03529	.02813
99	0/0	0/0	0/0	0/0	0/0	0/0
OVER-ALL	.01912	.01507	.02545	.01369	.02523	.01954
STANDARDIZED DEATH RATE	.01649	.01901	.02597	.02636	.02549	.01954
STANDARD (RATIO)	.84361	.97284	1.32859	1.34854	1.30450	
INDIRECT M.R.	.84071	.95420	1.29104	.73697	1.25339	

APPENDIX 1 TO CHAPTER IV-2

DETAILED DEFINITIONS OF ANESTHETIC PRACTICES

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Halothane: All operations with halothane that do not also use any of:
- ether,
- cyclopropane,
- methoxyflurane (code 2),
- Fluoromar (code 19), and
- miscellaneous (code 21).

Nitrous oxide-barbiturate: all operations with nitrous oxide-barbiturate that do not use any of:
- halothane,
- cyclopropane,
- ether,
- methoxyflurane,
- Fluoromar, and
- miscellaneous (code 21).

Cyclopropane: all operations with cyclopropane that do not use any of:
- halothane,
- ether,
- methoxyflurane,
- Fluoromar, and
- miscellaneous (code 21).

Ether: all operations with ether that do not use:
- halothane,
- cyclopropane,
- methoxyflurane,
- Fluoromar, or
- miscellaneous (code 21).

"Other": all operations not included above, i.e.:
- all operations using miscellaneous (code 21),
- all operations using methoxyflurane or Fluoromar,
- all operations using two or more of halothane, cyclopropane, or ether, and
- all operations using combinations or single agents that do not include
  - halothane,
  - nitrous oxide-barbiturate,
  - cyclopropane, or
  - ether.

APPENDIX 2 TO CHAPTER IV-2

DEFINITIONS OF VARIABLES

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Previous Operations: If the patient had had no operation (preceding the one that brought him into the Study) during the same or previous calendar month, this variable was scored "no previous op." If he had had one or more in that period in which halothane was used, the variable was scored "had halothane." If he had had one or more in that period, but none involved halothane, the variable was scored "no halothane."

Physical Status (Anesthetic Risk): Both names appear in the text and have the same meaning. The variable has eight classes:

0 - unknown;
1 - no complicating systemic disturbance, nonemergency;
2 - moderate complicating systemic disturbance, nonemergency;
3 - severe complicating systemic disturbance;
4 - extreme complicating systemic disturbance;
5 - no complicating or moderate complicating systemic disturbance, emergency;
6 - severe or extreme complicating systemic disturbance, emergency; and
7 - moribund.

Length: This variable has seven categories:

Unknown,
1 - 28 min,
29 - 58 min,
59 - 118 min,
119 - 238 min,
239 - 388 min, and
over 388 min.

Age: There are 11 categories: "unknown" and then by decades, less than 10 years old, 10 and over and less than 20, etc. The highest category is "over 90."

Sex: Male and female.

Year: The calendar years 1959, 1960, 1961, and 1962.

Institution: Thirty-four institutions have been arbitrarily assigned the numbers 1 through 34.

Operation: The classification of operations is based on the standard two-digit operation codes. Of the 100 operation codes (00 to 99), 12 did not appear in any institution (codes 11, 14, 19, 24, 29, 37, 61, 64, 82, 83, 96, and 97); 10 presented exactly one random case all together (codes 18, 35, 38, 49, 53, 69, 74, 78, 79, and 94); and one (91) had two random cases. All 23 of these operation codes were dropped. Operation code 31 (mammoplasty), with no deaths and 530 estimated exposed, was inadvertently omitted. This left 76 operation codes. Some tables present these 76 operation codes condensed to 25 groups of codes formed by combining the 76 in order of death rate. Most commonly in the Study, the 76 are grouped as high (codes 12, 33, 44, and 48), low (codes 1, 3, 55, 60, 65, 73, and 90), and middle (the remaining 65 codes).

APPENDIX 3 TO CHAPTER IV-2

ESTIMATION OF DEATH RATES

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Death rates are ordinarily estimated from counted data by dividing the number of deaths by the number exposed. In the National Halothane Study, the sample is used to estimate the number exposed during the period, but we have a count of all the deaths. The rate of sampling of operations, when averaged over hospitals, comes to about one case in 25. Consequently, in a portion of the population where few cases occur, sampling variation can produce cells with several observed deaths, but too few random cases to account for them; i.e., a cell can produce more deaths than the number of estimated exposed. Because we have occasion to look at many breakdowns of the data, with many cells, this situation can happen noticeably often, even though relatively infrequently.

When this occurs, the death rate given by deaths/(estimated exposed) either exceeds unity (a bizarre state of affairs), or is undefined because the denominator is zero.

Although reports of estimated death rates in excess of unity are not necessarily wrong or bad, carrying with them as they do their own urgent warning of unreliability, they can lead to misunderstanding, and they may not give as good an estimate of p, the death rate, as could be provided. By and large, in this report we have used the death-rate index,

$$\frac{\text{number of deaths}}{\text{number of deaths} + \text{estimated exposed}} = \frac{D}{D + EE}, \quad (1)$$

instead of the more usual D/EE. (Here D = number of deaths and EE = estimated exposed.) Estimate (1) has the advantage that if an estimate is made at all, as it would be unless the denominator were zero, the rate cannot exceed 1.00. Secondly, unless the death rates are very high or the cells very large, a commonly used measure of excellence, the mean square error, of this estimate of the true death rate, p, is smaller than that of the usual estimate. Most of our data concern death rates well under 0.5, and when the cells have large counts misunderstanding is not so likely.

Once one considers using estimate (1), the question arises whether augmenting EE in the denominator by a larger multiple of the number of deaths would give even more favorable results. We considered estimates of the form

$$f(c) = \frac{D}{cD + EE}, \quad (2)$$

and computed the mean square error (average value of $[f(c) - p]^2$) using the binomial distribution with number of exposed N = 25, 50, 100, 200, and 400 for various values of c and p. Estimate (2) was replaced by 1.00 when the numerator exceeded the denominator. Note that a random sampling rate of one in 25 corresponding to that used for hospitals in this Study was used here, so that, for example, when N = 25, the number observed in the sample has a probability of 0.37 of being zero. When both EE and D were zero, we made no contribution to the mean square error, on the grounds that one estimator was as bad as another in these straits.

For given values of p, N, and c, we computed the percentage reduction produced by estimate (2) compared with the mean square error given by that expression when c = 0. Then, for each p,c pair, we averaged the percent reduction over the five chosen values of N. These calculations led to the summary in Table 1.

TABLE 1.--SUMMARY OF AVERAGE PERCENTAGE REDUCTION IN MEAN SQUARE ERROR OF D/(cD + EE) FOR VARIOUS VALUES OF C, WITH THE AVERAGE OVER N = 25, 50, 100, 200, and 400.*

c \ p =	0.02	0.05	0.1	0.3	0.5	0.7
0.0	-	-	-	-	-	-
0.2	-1	-3	-7	-17	-21	-2
0.4	-2	-6	-14	-36	-31	3
0.6	-3	-9	-18	-37	-33	22
0.8	-4	-11	-22	-40	-29	50
1.0	-5	-13	-25	-41	-21	82
1.2	-27	-34	-44	-54	-25	106
1.4	-40	-46	-56	-60	-25	137
1.6	-49	-55	-64	-62	-12	169
1.8	-55	-61	-69	-62	-2	201
2.0	-60	-66	-73	-60	8	231
2.5	-67	-73	-79	-53	33	299
3.0	-72	-78	-81	-43	57	356
3.5	-75	-81	-82	-34	78	404
4.0	-78	-83	-81	-25	96	445
4.5	-80	-84	-80	-17	112	479
5.0	-81	-85	-73	-9	126	502

*A positive percentage means an increase; a negative percentage, a decrease.

The basic calculations leading to the table were made by William S. Mosteller.

The table shows that the mean square error for c = 1 is generally less than that for c = 0, except for high values of p. Indeed, from more detailed tables not presented here, up to p = 0.5, nearly all c's up to 1.00 produce reductions in mean square error for all N's up to 400. Thus, on the basis of mean square error, the use of c = 1 is preferable to c = 0. Just how large c might best be is a matter of judgment, but the table suggests that if a single value of c must be chosen, c might well have been larger than 1, perhaps 1.5 or even 2.0, for the death rates of the size we ordinarily discuss in connection with surgery. The table then offers a further reason for adding at least D to EE for the denominator of the estimate. It gives a better estimate of the death rate, and it keeps the estimated value within its natural bounds.

APPENDIX 4 TO CHAPTER IV-2

FORMULAS FOR DIRECT AND INDIRECT STANDARDIZATION USED IN CHAPTER IV-2

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Let the strata be indexed by $s = 1,\ldots, S$.
Let the anesthetic agents be indexed by $a = 1,\ldots, A$.
In the sth stratum we have:

d_{sa} = deaths in stratum s where agent a was used,

EE_{sa} = estimated exposed for agent a in stratum s,

$n_{sa} = d_{sa} + EE_{sa}$,

$d_{s+} = \sum_{a=1}^{A} d_{sa}$ deaths (all agents) in stratum s,

$n_{s+} = \sum_{a=1}^{A} n_{sa}$ deaths-plus-EE's (all agents) in stratum s,

$n_{++} = \sum_{s=1}^{S} n_{s+}$ total of all deaths-plus-EE's,

$d_{+a} = \sum_{s=1}^{S} d_{sa}$ deaths (all strata) for agent a, and

$p_{sa} = \dfrac{d_{sa}}{n_{sa}}$ estimated death rate in stratum s for agent a.

Then the directly standardized death rate (in terms of the system of strata $1,\ldots, S$) for agent a is given in the following expression:

$$p_a^* = \sum_{s=1}^{S} p_{sa} \frac{n_{s+}}{n_{++}}.$$

(Note: Where some p_{sa} was undefined, it was replaced in the expression for p_a^* by

$$p_{s.} = \frac{\sum_{a \neq a'} d_{sa}}{\sum_{a \neq a'} n_{sa}}.)$$

And the indirectly standardized mortality ratio for agent a is given in the following expression:

$$R_a^* = \frac{d_{+a}}{\sum_s n_{sa} \frac{d_{s+}}{n_{s+}}}.$$

Abstract of Chapter IV-3

Over-all adjusted summary rates can improve the comparison of death rates associated with different anesthetic agents by taking into account the effects of some of the underlying variables, but they do not indicate whether there are important reversals for a particular subsection of the population. The smoothed contingency-table analysis provides estimated rates that are more stable than the observed rates for each cell of a multidimensional contingency table. These rates can then be examined for trends and reversals within the population.

Smoothed rates have been computed for each of five anesthetic groups for various strata of four population segments. The segments were formed by splitting the operations into three groups according to their crude death rate: low, middle, and high. Cholecystectomies were treated separately, as well as being included in the middle-death-rate segment. The strata were defined by risk and age, and, where feasible, by sex and operation.

For each segment, the smoothed rates within strata did not vary greatly between agents. The reversals of ordering by agent between strata seemed to be random, rather than systematic.

For the low-death-rate operations and for the cholecystectomies, the highest rates most often occurred with the anesthetic group Other; and for the middle-death-rate operations, with cyclopropane and Other. The lowest rates for the low-death-rate operations most often occurred with ether and nitrous oxide-barbiturate; for the middle-death-rate operations, with ether, halothane, and nitrous oxide-barbiturate; and for the cholecystectomies, with halothane and nitrous oxide-barbiturate. Thus, for these three segments of data, nitrous oxide-barbiturate and halothane rates are usually among the lowest three, and cyclopropane rates are among the highest three. Ether is associated with the lowest rates for the low-death-rate and middle-death-rate operations, but with the second-highest rates for cholecystectomies. This may be a reflection of its uneven pattern of usage from one institution to another.

For the high-death-rate operations, this unevenness persists: ether is associated with the lowest rates for exploratory laparotomy (operation 44) and craniotomy (operation 12), is rarely used for heart and great vessel operations (operation 33), and seems to be associated with higher rates than halothane or nitrous oxide-barbiturate for large bowel operations (operation 48).

For the high-death-rate operations, the great increases in death rate for older persons and persons rated as poor risks are more striking than any differences between anesthetics. Rates for these operations, based on breakdowns that do not include anesthetic as a variable, point up these trends and provide baselines against which the effect of new techniques may be measured.

CHAPTER IV-3. SMOOTHED CONTINGENCY-TABLE ANALYSIS

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PURPOSE

Part IV of this report answers the comprehensive question: "How does the postoperative death rate after administration of halothane compare with the rates after other commonly used anesthetics?" The question is difficult to answer, because no single rate is associated with each anesthetic--instead, there is a range of rates. Even for the same operation, the risk of death for an individual patient depends far more on the patient's sex, physical status, and age, to mention but a few of the factors involved, than it does on the particular anesthetic used. Indeed, the physician thinks of his patient as a unique case. In other sections of this report, effort has nevertheless been directed toward providing a set of over-all rates that are comparable for each anesthetic. These have been computed by a variety of methods, but all methods have achieved comparability by the device of standardization, either direct or indirect.

No standardization would be necessary if there were no differences in the types of patients for whom each anesthetic was used, i.e., if the population did not differ between anesthetics. Even in the presence of differing population distributions, the answer to the primary question would not be difficult to obtain if, for every type of patient, the observed crude rates for each anesthetic always showed the same ordering by anesthetic. Standardization is a means of obtaining comparable over-all rates when the crude rates may not be comparable. They may not be comparable because:

(1) the rates for a single anesthetic differ between segments of the population,
(2) the relative frequency of use of anesthetics differs between segments of the population, and
(3) there are reversals in the crude rates for different anesthetics between segments of the population.

Over-all adjusted rates take into account the first two sources of noncomparability, and enable the primary public-health question to be answered. But the anesthesiologist about to administer an anesthetic is not as interested in an over-all rate based on the average for some hypothetical population as he is in the anesthetic likely to be best for this particular patient. He already knows the age, sex, operation, and physical status of the patient, and he may wish to use that knowledge in making his decision. Rates that are specific for each type of patient may help him.

The two questions are of course closely related. The first concern in answering the comprehensive question must be whether a higher death rate is in general associated with a particular anesthetic; but, as soon as we suspect that the relative rates for different anesthetics may be reversed for some segments of the population, then we must examine the data further. We try to determine whether the observed reversals could be merely random fluctuations or show clearly defined patterns. If patterns occur, then we may be able to define the segments of the population for whom a particular anesthetic is associated with a higher rate. For this purpose, also, we need to look at rates for each segment of the population.

The smoothed contingency-table analysis presented in this chapter is an attempt to provide such rates for each segment of the population; it therefore represents a long step, although not the whole trip, toward the objective appraisal of a unique case. The many strata provided represent single individuals better than usual, but, of course, the physician must take the further steps of recognizing and allowing for the variables not considered in the statistical tables.

If we introduce simultaneously several of the variables that describe attributes of the patient and that are known to affect death rates, we find that the population has been split into a great many segments, or "cells." Breaking up our sample observations into the corresponding number of dimensions and then looking at the observed death rate in each cell is unsatisfactory because the number of observations in each cell becomes small and so the crude rate is not very reliable. The smoothed contingency-table analysis "smooths" the data in the cells by replacing the original counts with fitted counts based on the one-, two-, and sometimes three-dimensional margins of the original table. The analysis gains strength by paying great attention to these margins of low dimension where the number of cases in a cell is usually fairly substantial. This method makes relatively few assumptions and, as described here, leans very hard on the original variables and the original distribution of the cases into their cells.

The smoothed rates are more reliable than the crude rates. In the process of computing them, care was taken to ensure that they did not depart systematically from the observed

rates and, hence, nullify the examination of trends or patterns to determine whether a particular subsection of the population had an unusually high rate with any one anesthetic. By providing both crude (observed) death rates and fitted death rates in the cells, we enable the reader to see the extent of the smoothing and to make alternative analyses if he prefers.

For the high-death-rate operations we have also provided a smoothed analysis that does not include anesthetic as a variable, because there may be some interest in the death rates associated with patients in various categories in these high-death-rate operations. This sort of use for the smoothed contingency-table analysis may turn out to be valuable in a variety of problems.

The contingency-table method is especially suited for the study of single cells and their comparison with one another. The method can, however, also be used as a means of defining the segments of the population that are subject to equal rates, and that can therefore be amalgamated for the purposes of deriving over-all adjusted rates. This is done in Chapter IV-5.

The reader who wishes to see results at once without a background of the method should turn to the second half of this chapter, beginning with the discussion of low-death-rate operations in particular. It should be kept in mind that death rates are computed as deaths/(deaths + estimated exposed), abbreviated as "D/D+EE."

GENERAL METHOD

In the contingency-table analysis, we examine separately the information on deaths and the information on operations performed (the random sample). Each of these two sets of data is laid out as a multidimensional contingency table. The number of dimensions of the table equals the number of variables being considered, such as age, sex, and anesthetic risk (physical status). Hereafter, "anesthetic risk" is abbreviated as "risk." Each variable has several categories and these jointly define the cells in the table. In a three-dimensional table with four categories of age, two of sex, and four of risk, the total number of cells is $4 \times 2 \times 4 = 32$.

As we have mentioned earlier, when the number of variables increases, the number of cells becomes very large, and for a fixed total number of observations, the number of estimated exposed per cell (or deaths per cell) must become small. Indeed, contingency tables based on several variables can easily have many empty cells.

Estimates based on small counts in individual cells have large sampling errors. Sometimes for a large contingency table, the method of analysis is merely to look at each two-way summary table (two-dimensional margin) to see whether the two variables are "correlated." One searches for a two-factor effect involving the two variables. In the three-dimensional case of age, sex, and risk, mentioned above, such a two-way table, or "face," might display, for example, risk against sex. The presence of a two-factor effect would imply that one sex had more high-risk operations than the other sex. The weakness of this approach has often been demonstrated: if, say, older persons have more high-risk operations than younger persons, an apparent two-factor effect between risk and sex might be due entirely to different age distributions for the two sexes, and would then disappear if the risk × sex table for each age were examined separately; on the other hand, a two-factor effect between risk and sex that appeared when each age was examined separately might disappear if all ages were combined and only the face table examined.

Thus, in the presence of three variables, we need to examine two-factor effects for each pair of variables at every level of the remaining variable. To illustrate, if age is variable 1, sex is variable 2, and risk is variable 3, the 1-2 table* for each level of 3 must be examined, and similarly the 1-3 table for each level of 2 and the 2-3 table for each level of 1. As an example, we give in Table 1 the four 2-3 tables (sex-risk), one for each level of variable 1 (age), for the deaths from the middle-death-rate operations.

Also given in the table is the ratio of females to males. If there were no 2-3 effect (sex-risk effect), then for any particular age this ratio would be the same for each risk level. In this example, there is a marked 2-3 effect: the ratio for age level 2 ranges between 0.68 and 0.99. Similarly, if there were no 1-2 effect (age-sex effect), then for any particular risk level the ratio would be the same for each age. We could examine these data for a 1-3 effect (age-risk effect) by computing similar ratios for successive age levels instead of successive sex levels, and again we would find that the effect was present.

Having established that all three two-factor effects are present, we can proceed to look for a three-factor effect. The absence of a three-factor effect implies that each two-factor effect is the same for each level of the third variable. In this example, it is most convenient to look at the 2-3 effect (sex-risk) and see whether it changes with age. To do this, we need to examine whether the ratio of the sex ratios for any two risk levels is the same for each age level. We can look, for instance, at the ratio of sex ratios for risk levels U and C. We see that this ratio is 0.78/0.65 for age level 1 and 0.99/0.68 for age level 2, and we conclude that the data show a marked three-factor effect.

If we had found that all three two-factor effects were present, but that each two-factor effect was of about the same magnitude for each level of the remaining variable, then we could have said that there was little evidence of a

*The abbreviation "1-2 table" denotes the two-way contingency table obtained when variable 1 is crossed with variable 2.

TABLE 1.--THE AGE × SEX × RISK DISTRIBUTION OF DEATHS FOR MIDDLE-DEATH-RATE OPERATIONS

Age level 1: 0-9 years + unknown
2: 10-49 years
3: 50-69 years
4: 70 years and older

Risk level U: unknown
A: anesthetic risks 1, 2, and 5
B: anesthetic risks 3, 4, and 6
C: anesthetic risk 7

Risk level	Age level 1		Age level 2		Age level 3		Age level 4	
	Female	Male	Female	Male	Female	Male	Female	Male
U	69	89	119	120	178	368	183	278
A	88	118	241	283	385	797	291	436
B	239	307	414	446	612	1131	596	867
C	41	63	90	132	105	215	133	181

SEX-RATIOS

Risk level	Age level 1	Age level 2	Age level 3	Age level 4
U	0.78	0.99	0.48	0.66
A	0.75	0.85	0.48	0.67
B	0.78	0.93	0.54	0.69
C	0.65	0.68	0.49	0.73

three-factor effect. In the absence of a three-factor effect, more stable estimates for every cell in the three-dimensional matrix could have been obtained by taking the two-factor effects as exactly the same for each level of the remaining variable. This exemplifies the source of strength mentioned at the beginning of this chapter.

This procedure can be extended to more than three variables: with five variables, for example, we can look at the five one-factor effects of each variable, the 10 two-factor effects, the 10 three-factor effects, the five four-factor effects, and the one five-factor effect. After a preliminary examination of the data, a mathematical model would be chosen that included only the effects that seemed to be large. To be effective in adding strength, such a model would include a selection of only the lower-order effects. Then estimates for every cell would be obtained in accordance with the chosen model. The observed values would be compared with the fitted values in each cell of the body of the table; if the differences were not large, then the model would be accepted as giving more stable cell estimates. Accepting the model for this purpose does not mean that we believe that all other effects are zero, but only that they are small enough that the cell estimates are improved by neglecting those effects. The situation is quite similar to the common one in regression, in which, to get improved precision, a straight-line or a quadratic function is deliberately fitted for estimation purposes, even when it is known that the true curve is more complex.

This, in very general terms, describes the approach adopted in the contingency-table analyses. Stable cell estimates have been obtained separately for the deaths and for the estimated exposed by fitting the same model to these two bodies of data, and then rates have been computed from these smoothed estimates.

MODELS AND NOTATION

The mathematical model of the contingency table in common use, and that used here, is the proportional one described by Birch (1). In a two-way table of sex × age, the absence of a two-factor effect means that the proportion of males is the same in every age category, and, of course, that the sexes have identical age distributions.

To discuss a three-variable model we need some notation. Let the count in the cell at the ith level of variable 1, the jth level of variable 2, and the kth level of variable 3 be denoted as x_{ijk}. The + subscript indicates that a variable has been summed over. Thus, if variable 3 has K categories,

$$x_{ij+} = x_{ij1} + x_{ij2} + \cdots + x_{ijK} = \sum_{k} x_{ijk},$$

$$x_{i++} = \sum_{j} x_{ij+},$$

and, if N is the total number of observations in the table,

$$x_{+++} = \sum_i x_{i++} = N;$$

x_{+j+} and x_{++k} are defined similarly.

We have used the notation m_{ijk} to represent the fitted count in each cell. The "fitted" or "smoothed" values are obtained by fitting a theoretical model to the data. Thus, the fitted m_{ijk} are maximum likelihood estimates of the theoretical values postulated by the model. We have also used m_{ijk} to denote the theoretical values, in the belief that this will be less confusing to the reader than introducing yet another notation.

Suppose that, on examining the data of Table 1, we had found no large two-factor or three-factor effects. Then we could have replaced the observed cell estimates, x_{ijk}, with fitted cell estimates, m_{ijk}, which exhibited no two-factor or three-factor effects at all. This is equivalent to saying that each m_{ijk} is proportional to the product of its three marginal proportions:

$$m_{ijk} = \frac{x_{i++}}{N} \times \frac{x_{+j+}}{N} \times \frac{x_{++k}}{N} \times N, \quad \begin{matrix} i = 1,2,\ldots,I, \\ j = 1,2,\ldots,J, \\ k = 1,2,\ldots,K. \end{matrix} \qquad (1)$$

For example, x_{i++}/N could be the proportion of 50-year-olds, x_{+j+}/N the proportion of males, and x_{++k}/N the proportion of low-risk patients.

When we examined the data to see whether two-factor effects existed, we looked at ratios; then, to see whether three-factor effects existed, we looked at ratios of ratios. If we had first taken the logarithm of every cell entry, we could have looked instead at logarithmic sums and differences. The smoothed estimates can also be expressed additively in the logarithmic scale. If we take logarithms of both sides of Eq. 1, we have:

$$\log m_{ijk} = \log x_{i++} + \log x_{+j+} + \log x_{++k} - 2 \log N. \qquad (2)$$

An attraction of the additive form is that it brings with it the usual analysis of variance notions of grand mean, row effect, column effect, layer effect, and interactions of various orders. We can achieve precisely these ideas in the logarithmic model by converting to Birch's notation, shortly to be discussed. In this notation, if we do not distinguish between the theoretical values and our estimates of them, we can write Eq. 2 as:

$$\log m_{ijk} = u + u_{1(i)} + u_{2(j)} + u_{3(k)}. \qquad (3)$$

Here we only sketch the ideas of the u's; a fuller development is given in Appendix 1. In this notation, u is the grand mean of the logarithm of the theoretical counts in all IJK cells; $u = \sum_{i,j,k} \log m_{ijk}/IJK$, all $m_{ijk} > 0$. Similarly, $(u + u_{1(i)})$ is the mean of the logarithm of the counts in all JK cells at level i of variable 1, $(\sum_{j,k} \log m_{ijk}/JK)$; thus, $u_{1(i)}$ is the deviation of this mean from u, the grand mean. For variables 2 and 3, $u_{2(j)}$ and $u_{3(k)}$ are similarly defined.

Because the values of $u_{1(i)}$, $u_{2(j)}$, and $u_{3(k)}$ are deviation scores,

$$\sum_i u_{1(i)} = \sum_j u_{2(j)} = \sum_k u_{3(k)} = 0.$$

The advantage of changing to this notation is that it can be extended to include multifactor effects by adding further terms, which are again deviation scores. In Eq. 2 we were able to adjust for the fact that $\log x_{i++}$, $\log x_{+j+}$, and $\log x_{++k}$ were not deviation scores by subtracting 2 log N. We cannot do this so simply in models that include all the two-factor effects. For example, in the three-dimensional case, if all three two-factor effects were present, but the three-factor effect were so small that it could be neglected, the model could be written:

$$\log m_{ijk} = u + u_{1(i)} + u_{2(j)} + u_{3(k)} + [u_{12(ij)} + u_{13(ik)} + u_{23(jk)}]. \qquad (4)$$

The first three subscripted u-terms are defined as deviations from u. The three additional terms in brackets represent the three two-factor effects; $u_{12(ij)}$ represents the two-factor effect (joint effect) of variables 1 and 2 and can assume a different value for each combination of categories i and j of these variables. Thus, if variable 1 has two categories and variable 2 has three categories, the values of u_{12} can be represented by a 2×3 matrix. An example is given in Appendix 1. In this 2×3 matrix of values of u_{12}, every row and every column totals zero, because these two-dimensional terms are again deviations from the linear terms. The number of degrees of freedom associated with the matrix is $(2-1) \times (3-1) = 2$.

To obtain these estimates, we would use the three observed two-dimensional faces with entries x_{ij+}, x_{+jk}, and x_{i+k}. The fitted m_{ijk} would be obtained by an iterative process and would add to the same totals, that is:

$$\begin{aligned} m_{ij+} &= x_{ij+} \quad \text{for all } i,j, \\ m_{+jk} &= x_{+jk} \quad \text{for all } j,k, \\ m_{i+k} &= x_{i+k} \quad \text{for all } i,k. \end{aligned}$$

Thus, although it is necessary to change the notation to express the model, the fitted values

are computed entirely from the summary x's. That is true for all models of this type that involve multifactor effects of lower order than the dimensionality of the table. The computations are carried out entirely from the summary edges, two-dimensional faces, or, when needed, three-dimensional faces that are involved in the lower-order effects and without further reference to the individual cells, once the summary statistics are obtained by addition.

Table 2 shows the summary two-dimensional faces for the age-sex-risk data on deaths presented in Table 1. These are the summary faces that would be used to fit the model given in Eq. 4. As we observed from our inspection of Table 1, we would not expect the model given in Eq. 4 to fit these data well, because the data show a large three-factor effect. When fitting a five-variable model to the middle-death-rate data, we included all 10 three-factor effects, and the entire 32 cells given in Table 1 constituted one of the summary three-dimensional faces used. With other sections of the data, we have found that it was sufficient to include only two-factor effects. When the effects fitted are of low order, the summary faces have fewer cells and the entries in each summary cell are relatively stable.

TABLE 2.--THE FACES FOR THE AGE × SEX × RISK DISTRIBUTION OF DEATHS FOR THE MIDDLE-DEATH-RATE OPERATIONS

Age level 1: 0-9 years + unknown
2: 10-49 years
3: 50-69 years
4: 70 years and older

Risk level U: unknown
A: anesthetic risks 1, 2, and 5
B: anesthetic risks 3, 4, and 6
C: anesthetic risk 7

The 1-2 table (age × sex):

Age level	Female	Male
1	437	577
2	864	981
3	1280	2511
4	1203	1762

The 1-3 table (age × risk):

Age level	Risk level			
	U	A	B	C
1	158	206	546	104
2	239	524	860	222
3	546	1182	1743	320
4	461	727	1463	314

The 2-3 table (sex × risk):

Sex	Risk level			
	U	A	B	C
Female	549	1005	1861	369
Male	855	1634	2751	591

In one analysis for the cholecystectomies, for example, six variables were considered: three operation codes, two periods, three risk categories, three age groups, two sexes, and five anesthetic agents, for a total of 540 cells. When we scattered 672 deaths into 540 cells, many cells remained empty. The model chosen involved eight of the possible 15 two-factor effects and none of the three-factor, four-factor, five-factor, or six-factor effects. The eight relevant summary faces provided all the necessary information for fitting the model. (The one-factor effects have always been included, but these one-dimensional totals can be derived from the face totals.) Thus, the largest face had $3 \times 5 = 15$ cells, and the distribution of the 672 deaths put a fairly large count into every cell of every face, so estimates could be obtained for all 540 elementary cells.

Appendix 1 gives details of the method of selecting a model, the method of computing estimates from the model, and the criteria for deciding whether the model is satisfactory.

SEGMENTS OF DATA ANALYZED

Three death-rate groups divided the operations into three segments:

(1) the seven low-death-rate operations,
(2) the four high-death-rate operations, and
(3) the remaining (middle-death-rate) operations (see Chapter IV-2 for description).

For our contingency-table method, we analyzed these three death-rate groups separately. In addition, we made a separate analysis of cholecystectomies, which were represented by three codes of operations in the middle-death-rate segment:

code 40: cholecystectomy alone,
code 41: cholecystectomy and/or bile duct, and
code 42: cholecystectomy and/or bile duct and other major procedures.

Cholecystectomies were chosen for special consideration because they form a fairly standard group of operations that are performed frequently in most institutions. Furthermore, we believed that they could be expected to show the deleterious effects of halothane if such effects existed.

Risk 7 cases and deaths were not used in the cholecystectomy analysis, because they were moribund cases and it would be reasonable to analyze them separately; however, the number of cases (six observed cases, which means about 150 estimated exposed and 52 deaths) was so small that a satisfactory separate analysis cannot be made.

The numbers of deaths, randoms (i.e., cases in the random sample), and estimated exposed for each segment are shown in Table 3. This table also gives the number of categories for each variable considered in each segment, the resulting total number of cells, and, where pertinent, the number of the table in which the death rates are presented. The definition of categories varied slightly in the different segments, as discussed below and summarized in Table 5. The models fitted are given in Table 4.

SELECTION OF VARIABLES

We selected five variables as offering satisfactory data, being important, and being feasible for control: agent, sex, risk, age, and operation. Length of operation would have given an analysis of some value, but circumstances prevented its use in the smoothed contingency-table analysis. Other methods do use length for some analyses. Because the sample size was not large enough, it was not feasible to consider more than six variables at once, and for some segments of the data even six represented too fine a breakdown.

Although other methods of analysis showed important differences between institutions (see Chapter IV-6), we could not include institution as a variable in the contingency-table method. Treating each institution separately makes too many cells with too few operations per cell; attempts to put institutions into homogeneous classes failed.

We also analyzed the middle-risk operations, omitting the effect of sex differences. In analyzing the low-risk operations, we pooled the seven operation codes.

CATEGORIES PER VARIABLE

Whenever the variable "agent" is used, it has five categories, corresponding to the five common-practice groups. The principal constituents were:

agent 1: halothane,
agent 2: nitrous oxide-barbiturate (N-B),
agent 3: cyclopropane,
agent 4: ether, and
agent 5: Other and combinations of above.

As explained in Appendix 1 to Chapter IV-2, these principal constituents are seldom, if ever, used alone. We will, however, in our discussion use them as the names for our five categories and, for the sake of brevity, speak of category 5 as "Other."

The dichotomous variable "sex" has females in the first category, males in the second. This variable is used for all segments except models B for middle and high death rate.

In many but not all institutions, it is customary to rate the patient, before operation, on a seven-point scale of operative risk, called "anesthetic risk" or "physical status." Because this information was not available for all institutions, there is also a large category of "unknown" risk. For high- and middle-death-rate operations, the risk classifications have been grouped according to their associated death rates. Thus, low-risk emergencies have been grouped with low-risk nonemergencies, leading to the following categories:

category U: unknown;
category A: risks 1, 2, and 5;
category B: risks 3, 4, and 6; and
category C: risk 7.

For cholecystectomies, category C was omitted.

For the low-death-rate operations, category C was omitted and the emergency operations were separated from the nonemergency, so that the categories were:

category U: unknown,
category A1: risks 1 and 2,
category B1: risks 3 and 4,
category A2: risk 5, and
category B2: risk 6.

The age categories were:

ages 0 - 9 years plus a very few unknown ages,
ages 10 - 49 years,
ages 50 - 69 years, and
ages 70 years and older.

For the cholecystectomies, the count in the first of these categories was small and so was combined with that in the next category.

The variable "operation" was omitted from the low-death-rate analysis. For cholecystectomies, this variable had three categories; codes 40, 41, and 42. The high-death-rate segment had four categories: codes 48, 44, 12, and 33, in

TABLE 3.--BREAKDOWN OF DATA INTO SEGMENTS AND CELLS

Death-rate segment	Deaths	Observed cases	Estimated exposed	Categories per variable					Total no. of cells	Table of rates
				Agent	Sex	Risk	Age	Operation		
Low*	803	15,577	366,189	5	2	5	4	--	200	6
Middle, model A	9615	19,490	426,033	5	2	4	4	5	800	(not given)
Middle, model B	9615	19,490	426,033	5	--	4	4	5	400	16
Cholecystectomy*	672	1,220	27,620	5	2	3	3	3	270	21
High, model A	6354	2,875	61,720	--	2	4	4	4	128	24
High, model B	6354	2,875	61,720	5	--	4	4	4	320	26

*Risk 7 cases are omitted from the low-death-rate and cholecystectomy segments.

TABLE 4.--MODELS FITTED

Death-rate segment	No. of variables	1-dimensional margins	2-dimensional faces	3-dimensional faces
Low	4	all 4	all 6	none
Middle, model A	5	all 5	all 10	all 10
Middle, model B	4	all 4	all 6	all 4
Cholecystectomy	5	all 5	agent × sex	none
			agent × risk	
			agent × age	
			agent × operation	
			risk × age	
			risk × operation	
			age × operation	
High, model A	4	all 4	all 6	none
High, model B*	4	all 4	all 6	

*Special device used of introducing constants into all cells, fitting, then removing constants.

TABLE 5.--SUMMARY OF VARIABLES USED AND CATEGORIES FOR EACH VARIABLE FOR EACH SEGMENT OF DATA

Standard categories			
Agent	Sex	Risk	Age
1 = halothane 2 = nitrous oxide-barbiturate 3 = cyclopropane 4 = ether 5 = Other	Female Male	U = unknown A1 = risks 1 + 2 B1 = risks 3 + 4 A2 = risk 5 B2 = risk 6 C = risk 7	0 - 9 + unknown 10 - 49 50 - 69 70 +

Categories used					
Death-rate segment	Agent	Sex	Risk	Age	Operation
Low	standard	standard	standard except C omitted	standard	7 operation codes combined
Middle, model A	standard	standard	U = unknown A = A1 + A2 B = B1 + B2 C = risk 7	standard	5 categories of increasing death rate
Middle, model B	standard	omitted	U = unknown A = A1 + A2 B = B1 + B2 C = risk 7	standard	5 categories of increasing death rate
Cholecystectomy	standard	standard	U = unknown A = A1 + A2 B = B1 + B2 C omitted	0 - 49 + unknown 50 - 69 70 +	code 40 code 41 code 42
High, model A	omitted	standard	U = unknown A = A1 + A2 B = B1 + B2 C = risk 7	standard	code 48 code 44 code 12 code 33
High, model B	standard	omitted	U = unknown A = A1 + A2 B = B1 + B2 C = risk 7	standard	code 48 code 44 code 12 code 33

order of increasing death rate. For the middle-death-rate operations, we condensed the 25-category code used in other analyses to five categories by adding successive groups of five. We derived this 25-category code by arranging all operations in order of increasing crude death rate and then combining consecutive operations so that each group had approximately the same number of deaths.

Table 5 summarizes these definitions of variables and categories.

READING AND CONSIDERING CELLS OF TABLES

In every cell of the tables of death rates for the smoothed contingency-table analysis, we present:

(1) observed death rate,
(2) fitted number of deaths,
(3) fitted number of randoms (EE), and
(4) fitted death rate.

Observed death rates are computed from deaths/(deaths + EE), and the fitted death rates from fitted deaths/(fitted deaths + fitted EE). In interpreting these data, a number of cautions are in order.

The method of smoothed contingency tables improves the stability of estimated death rates, but here it cannot do quite as much as it would in some studies because of the sampling design. Because hospitals contributed equal numbers of randomly chosen cases, rather than equal proportions of their own cases, each case in the sample must be weighted by a factor depending on the total number of operations performed in the hospital to give the estimated exposed. This factor varies between 5 and 75. It was necessary to do this weighting before fitting the model. Thus, although the face or cube summary cells

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from which the model estimates were derived seemed to be larger than those for the deaths, they were subject to greater sampling variability. A cell entry of 200 estimated exposed, for instance, could represent on the average only eight sample cases, whereas a cell of the same size for deaths would represent 200 independent pieces of information. This means that any measure of deviation between observed and fitted cell values will be large for the estimated exposed (see Appendix 1). From the point of view of interpretation of the results, it means that, even when the model has been fitted, rates based on fewer than 100 estimated exposed (about four randoms) are subject to such large errors that they are of little value taken individually.

The method ensures that the total number of entries in each cell of each two-way or three-way summary table used is unaltered; if the model predicts too many observations in one cell, it necessarily predicts too few in another for the margins used. The fitted cell entries depend entirely on the summary tables. Occasionally, even with condensation of categories and inclusion of only the most important variables, the cells of the summary tables are small or empty; this is particularly true of the high-death-rate operations. When the cell estimates are small, they are obtained from small cells in the summary tables. Small cells are not as reliable as large cells; consequently, the estimates derived from them are not as reliable. This is particularly true of the estimated exposed. Thus, when the estimated deaths and estimated exposed are combined to give rates in each cell, the rates will not be reliable if the number of exposed is small. This will show up in the tables of rates in the form of large differences between neighboring cells.

LOW-DEATH-RATE OPERATIONS

The variables selected were sex, age (four categories), and risk (five categories), giving 40 cells for each of five agents. Two models were fitted, one using all two-dimensional faces and the other all three-dimensional faces. The former was judged to give an adequate fit and did not introduce empty cells, as did the latter; the following discussion is therefore based on the fit using two-dimensional faces.

Table 6 shows both the observed and the fitted death rates in detail. But much can be learned from the shorter summary tables (Tables 7 through 15). For this segment of the data, risk categories A1 (elective, anesthetic risks 1 and 2), A2 (emergency, anesthetic risk 5), B1 (elective, anesthetic risks 3 and 4), and B2 (emergency, anesthetic risk 6) are used.

Comparison of Halothane (Agent 1) with Nitrous Oxide-Barbiturate (Agent 2)

The fitted rates of Table 7 for halothane and for nitrous oxide-barbiturate come from cells of Table 6 in which at least one of the two agents has at least 2500 estimated exposed. The numbers in parentheses are the numbers of estimated exposed in hundreds. Nitrous oxide-barbiturate appears more popular than halothane, but both were used extensively. Observe that, although nitrous oxide-barbiturate generally had the lower death rate, the values are rather close together, except for risk U.

Of the 40 pairs of cells shown in the complete table, halothane had the higher observed (unsmoothed) death rate in 22 pairs and nitrous oxide-barbiturate in 14 pairs, and there were four ties at zero deaths. Here, for assessing consistency, observed rates seem more appropriate, because smoothed rates may offer misleading consistency. Risks B1, A2, and B2 have fewer cases, and they need a separate summary. Table 8 gives rates added over age and sex. These will be the same for fitted and observed, because the risk × agent table was one of the configurations fitted. It shows that the rates are close together for the two agents. A difference of 1 percent, as for risk B2, between the death rates for halothane and nitrous oxide-barbiturate matters, if it is real, but its sampling error is large. As a grand summary, experience with nitrous oxide-barbiturate has produced a slightly lower rate than halothane.

Comparison of Halothane (Agent 1) with Cyclopropane (Agent 3)

The fitted rates of Table 9 for halothane and cyclopropane come from cells of Table 6 in which at least one of the two agents has at least 2500 estimated exposed. Table 9 shows the two agents to be very closely matched, with differences of no more than a few hundredths of 1 percent. Cyclopropane looks slightly better over-all.

Table 10 compares the halothane and cyclopropane rates for risks B1, A2, and B2. Again, the rates for the two agents are close to one another. Except for the death-rate excess of 0.8 percent for halothane in risk B2 of Table 10, Tables 9 and 10 leave the two agents closely matched.

Comparison of Halothane (Agent 1) with Ether (Agent 4)

The fitted rates of Table 11 for halothane and ether come from cells of Table 6 in which at least one of the two agents has at least 2500

TABLE 6.--OBSERVED RATES AND RATES FITTED TO 4 VARIABLES: AGENT, RISK, SEX, AND AGE

LOW DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
			FEMALE					MALE		
RISK U ,AGE 0- 9										
OBS RATE	0.00613	0.	0.00169	0.	0.00098	0.00084	0.	0.00385	0.00039	0.00070
FIT DEAD	4.0	0.3	3.0	1.8	3.1	3.4	0.2	1.5	1.1	2.6
FIT EE	1240.6	269.7	1015.7	1929.5	2204.8	2007.3	302.4	718.5	2853.6	3045.2
FIT RATE	0.00319	0.00098	0.00293	0.00095	0.00140	0.00170	0.00060	0.00213	0.00040	0.00085
RISK U ,AGE 10-49										
OBS RATE	0.00177	0.00083	0.00166	0.00237	0.00167	0.00135	0.00071	0.	0.	0.00152
FIT DEAD	7.6	3.8	7.5	1.5	3.6	3.8	1.5	2.3	0.6	1.8
FIT EE	4143.7	8164.9	5553.8	1464.4	1677.9	1841.6	2514.5	1079.1	594.9	636.5
FIT RATE	0.00183	0.00046	0.00135	0.00103	0.00217	0.00208	0.00060	0.00210	0.00093	0.00283
RISK U ,AGE 50-69										
OBS RATE	0.00292	0.00211	0.00302	0.00272	0.01322	0.00629	0.00106	0.00989	0.	0.02287
FIT DEAD	5.3	4.0	6.0	1.0	4.2	6.4	3.9	4.4	0.9	5.0
FIT EE	1304.1	2582.3	1388.5	343.0	462.4	1248.2	1712.6	581.0	300.1	377.7
FIT RATE	0.00404	0.00156	0.00431	0.00284	0.00890	0.00513	0.00227	0.00749	0.00287	0.01294
RISK U ,AGE 70+										
OBS RATE	0.01386	0.01685	0.01929	0.01323	0.00392	0.02670	0.00844	0.13866	0.01323	0.10319
FIT DEAD	5.1	4.6	6.4	0.5	2.8	9.4	6.7	7.0	0.6	5.0
FIT EE	211.5	557.7	200.4	77.0	136.9	277.0	506.2	114.8	92.1	153.0
FIT RATE	0.02364	0.00823	0.03076	0.00630	0.01990	0.03266	0.01305	0.05716	0.00697	0.03150
RISK A1,AGE 0- 9										
OBS RATE	0.00081	0.00080	0.00090	0.00040	0.00051	0.00012	0.	0.00084	0.00040	0.00022
FIT DEAD	6.5	0.9	3.2	5.6	3.9	3.3	0.4	1.0	2.1	2.0
FIT EE	5568.3	1002.0	3580.7	9349.0	10413.1	8505.5	1060.6	2391.2	13052.5	13577.1
FIT RATE	0.00116	0.00091	0.00090	0.00060	0.00038	0.00039	0.00035	0.00041	0.00016	0.00015
RISK A1,AGE 10-49										
OBS RATE	0.00049	0.00035	0.00051	0.00074	0.00064	0.00060	0.00037	0.00099	0.	0.
FIT DEAD	16.2	17.0	10.6	6.1	6.1	4.9	4.1	1.9	1.3	1.8
FIT EE	25609.0	41768.3	26958.3	9769.9	10911.2	10744.0	12143.2	4944.8	3746.4	3907.4
FIT RATE	0.00063	0.00041	0.00039	0.00062	0.00056	0.00045	0.00033	0.00039	0.00036	0.00046
RISK A1,AGE 50-69										
OBS RATE	0.00211	0.00186	0.00153	0.00328	0.00311	0.00196	0.00207	0.00084	0.00121	0.00306
FIT DEAD	15.6	25.0	11.7	5.5	9.6	11.3	14.4	5.1	2.9	6.8
FIT EE	7756.0	12712.0	6485.8	2202.3	2893.5	7007.4	7958.8	2561.9	1818.6	2231.5
FIT RATE	0.00201	0.00197	0.00181	0.00247	0.00330	0.00162	0.00180	0.00199	0.00158	0.00305
RISK A1,AGE 70+										
OBS RATE	0.00614	0.00995	0.01013	0.00252	0.00268	0.01094	0.00394	0.00233	0.	0.00607
FIT DEAD	7.7	14.6	6.3	1.4	3.3	8.4	12.6	4.1	1.1	3.5
FIT EE	1010.7	2206.1	752.2	397.0	688.3	1249.9	1890.5	406.7	448.8	726.5
FIT RATE	0.00756	0.00658	0.00833	0.00348	0.00473	0.00667	0.00662	0.01004	0.00244	0.00478

Table 6 (Cont'd)

LOW DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
	FEMALE					MALE				
RISK B1,AGE 0- 9										
OBS RATE	0.04530	0.07166	0.03256	0.01078	0.02583	0.00969	0.01678	0.04056	0.02208	0.00910
FIT DEAD	5.8	0.6	3.0	3.9	4.9	4.4	0.4	1.4	2.1	3.6
FIT EE	141.0	18.7	77.0	172.2	218.5	204.8	18.8	48.9	228.6	270.9
FIT RATE	0.03962	0.03085	0.03766	0.02190	0.02189	0.02097	0.01854	0.02708	0.00915	0.01318
RISK B1,AGE 10-49										
OBS RATE	0.01110	0.01309	0.01389	0.02668	0.05642	0.02058	0.01618	0.	0.	0.04653
FIT DEAD	14.6	11.1	9.9	4.2	7.6	6.5	3.9	2.6	1.3	3.3
FIT EE	771.2	925.3	689.0	214.0	272.2	307.7	255.8	120.2	78.0	92.7
FIT RATE	0.01855	0.01187	0.01419	0.01915	0.02705	0.02059	0.01504	0.02145	0.01695	0.03431
RISK B1,AGE 50-69										
OBS RATE	0.01501	0.01577	0.01916	0.02018	0.05066	0.03019	0.02077	0.04588	0.00912	0.03337
FIT DEAD	13.0	15.1	10.1	3.5	11.0	13.9	12.8	6.5	2.7	11.5
FIT EE	761.7	918.3	540.6	157.3	235.4	654.4	546.7	203.1	123.5	172.6
FIT RATE	0.01675	0.01619	0.01842	0.02148	0.04462	0.02073	0.02284	0.03096	0.02120	0.06253
RISK B1,AGE 70+										
OBS RATE	0.03236	0.01968	0.02710	0.00598	0.02393	0.04666	0.02703	0.05569	0.01635	0.02848
FIT DEAD	8.0	11.1	6.9	1.1	4.7	12.9	14.1	6.6	1.3	7.4
FIT EE	329.9	529.6	208.3	94.2	186.1	387.9	431.6	107.1	101.3	186.8
FIT RATE	0.02377	0.02048	0.03189	0.01157	0.02468	0.03213	0.03156	0.05796	0.01251	0.03814
RISK A2,AGE 0- 9										
OBS RATE	0.	0.	0.	0.	0.01083	0.	0.	0.	0.	0.
FIT DEAD	0.1	0.0	0.3	0.3	0.4	0.1	0.0	0.2	0.2	0.4
FIT EE	176.0	31.2	279.5	55.3	279.3	151.6	18.6	105.3	43.6	205.4
FIT RATE	0.00077	0.00063	0.00099	0.00482	0.00158	0.00081	0.00076	0.00143	0.00406	0.00192
RISK A2,AGE 10-49										
OBS RATE	0.00077	0.	0.	0.05747	0.00120	0.00191	0.	0.	0.	0.
FIT DEAD	0.4	0.4	1.0	0.3	0.7	0.2	0.2	0.3	0.1	0.4
FIT EE	1705.1	2737.7	4432.3	121.8	616.3	403.4	448.9	458.5	26.3	124.5
FIT RATE	0.00022	0.00014	0.00022	0.00258	0.00120	0.00049	0.00038	0.00069	0.00464	0.00312
RISK A2,AGE 50-69										
OBS RATE	0.	0.	0.02347	0.	1.00000	0.	0.00959	0.10981	1.00000	0.07082
FIT DEAD	0.5	0.8	1.5	0.4	1.6	0.6	0.8	1.2	0.4	2.1
FIT EE	88.8	143.3	183.4	4.7	28.1	45.3	50.6	40.9	2.2	12.2
FIT RATE	0.00558	0.00570	0.00829	0.07746	0.05503	0.01402	0.01633	0.02820	0.14452	0.14499
RISK A2,AGE 70+										
OBS RATE	0.	0.07215	0.04239	0.	0.	0.08013	1.00000	1.00000	0.	1.00000
FIT DEAD	0.4	0.7	1.2	0.1	0.8	0.7	1.1	1.4	0.2	1.5
FIT EE	12.6	27.1	23.2	0.9	7.3	8.8	13.1	7.1	0.6	4.3
FIT RATE	0.02709	0.02467	0.04849	0.13450	0.09875	0.07185	0.07439	0.16253	0.25542	0.25929

Table 6 (Cont'd)

LOW DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
			FEMALE					MALE		
RISK B2,AGE 0- 9										
OBS RATE	0.	0.	0.20636	1.00000	1.00000	0.08485	0.	1.00000	0.02593	0.01750
FIT DEAD	1.4	0.1	1.5	0.7	1.6	3.0	0.2	2.0	1.2	3.4
FIT EE	20.0	2.0	23.3	11.6	33.4	27.5	1.9	14.0	14.6	39.1
FIT RATE	0.06336	0.04947	0.06105	0.05898	0.04557	0.09727	0.08654	0.12424	0.07343	0.08036
RISK B2,AGE 10-49										
OBS RATE	0.00561	0.00763	0.00586	0.	0.01249	0.03808	0.16402	0.03882	0.	0.34998
FIT DEAD	3.4	2.0	5.0	0.8	2.5	4.4	2.0	3.9	0.7	3.1
FIT EE	373.0	345.5	710.2	49.3	141.9	140.7	90.3	117.1	17.0	45.7
FIT RATE	0.00911	0.00579	0.00704	0.01594	0.01728	0.03340	0.02220	0.03207	0.04204	0.06449
RISK B2,AGE 50-69										
OBS RATE	0.04305	0.05747	0.08609	0.	0.	1.00000	0.07139	0.12609	0.07816	0.04797
FIT DEAD	1.3	1.2	2.2	0.3	1.6	4.1	2.9	4.1	0.6	4.7
FIT EE	48.2	44.9	72.9	4.7	16.0	39.1	25.2	25.9	3.5	11.1
FIT RATE	0.02654	0.02559	0.02954	0.05658	0.08864	0.09415	0.10268	0.13714	0.15362	0.29876
RISK B2,AGE 70+										
OBS RATE	0.21211	0.	0.13810	0.	0.07152	0.07093	0.17949	0.24348	0.	1.00000
FIT DEAD	1.3	1.4	2.4	0.1	1.1	6.2	5.2	6.8	0.5	5.0
FIT EE	33.6	41.7	45.3	4.6	20.4	37.4	32.1	22.0	4.6	19.4
FIT RATE	0.03787	0.03261	0.05121	0.03128	0.05054	0.14138	0.13879	0.23619	0.09684	0.20373

TABLE 7.--FITTED DEATH RATES IN LARGE CELLS FOR LOW-DEATH-RATE OPERATIONS, HALOTHANE COMPARED WITH NITROUS OXIDE-BARBITURATE

Risk level: U = unknown
A1 = risks 1 + 2
A2 = risk 3

Risk	Age	Female		Male	
		H	N-B	H	N-B
U	10-49	0.0018 (41)*	0.0005 (82)	0.0021 (18)	0.0006 (25)
U	50-69	0.0040 (13)	0.0016 (26)		
A1	0-9	0.0012 (56)	0.0009 (10)	0.0004 (85)	0.0004 (11)
A1	10-49	0.0006 (256)	0.0004 (418)	0.0005 (107)	0.0003 (121)
A1	50-69	0.0020 (78)	0.0020 (127)	0.0016 (70)	0.0018 (80)
A2	10-49	0.0002 (17)	0.0001 (27)		

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 8.--SUMMARY OF FITTED DEATH RATES FOR LOW-DEATH-RATE OPERATIONS OVER ALL AGES FOR RISK CATEGORIES B1, A2, and B2, HALOTHANE COMPARED WITH NITROUS OXIDE-BARBITURATE

Risk level: B1 = risks 3 + 4
A2 = risk 5
B2 = risk 6

Risk	H	N-B
B1	0.0221 (36)*	0.0190 (36)
A2	0.0011 (26)	0.0012 (34)
B2	0.0349 (7)	0.0258 (6)

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 9.--FITTED DEATH RATES IN LARGE CELLS FOR LOW-DEATH-RATE OPERATIONS, HALOTHANE COMPARED WITH CYCLOPROPANE

Risk level: U = unknown
A1 = risks 1 + 2
A2 = risk 3

Risk	Age	Female		Male	
		H	C	H	C
U	10-49	0.0018 (41)*	0.0014 (56)		
A1	0-9	0.0012 (56)	0.0009 (36)	0.0004 (85)	0.0004 (24)
A1	10-49	0.0006 (256)	0.0004 (270)	0.0005 (107)	0.0004 (49)
A1	50-69	0.0020 (78)	0.0018 (65)	0.0016 (70)	0.0020 (26)
A2	10-49	0.0002 (17)	0.0002 (44)		

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 10.--SUMMARY OF FITTED DEATH RATES FOR LOW-DEATH-RATE OPERATIONS OVER ALL AGES FOR RISK CATEGORIES B1, A2, and B2, HALOTHANE COMPARED WITH CYCLOPROPANE

Risk level: B1 = risks 3 + 4
A2 = risk 5
B2 = risk 6

Risk	H	C
B1	0.0221 (36)*	0.0235 (20)
A2	0.0011 (26)	0.0013 (55)
B2	0.0349 (7)	0.0270 (10)

*Numbers in parentheses are estimated exposed in hundreds.

estimated exposed. The differences are small, with ether showing lower rates for the risk U and young risk A1 patients. Table 12 compares the agents for risks B1, A2, and B2; the two agents are extremely closely matched. Elsewhere, we explain that our results for ether are more uncertain than for the other anesthetics because ether is little used by some institutions.

Comparison of Halothane (Agent 1) with Other (Agent 5)

The fitted rates of Table 13 for halothane and Other come from cells of Table 6 in which at least one of the two agents has at least 2500 estimated exposed. It does not seem worthwhile to produce the death-rate comparison for risks B1, A2, and B2, because the numbers of estimated exposed are small. Although closely matched, Other had a lower rate for the young, halothane a slightly lower rate for the older patients.

Discussion

Inspection of the five agents for each risk-age-sex category shows that the estimated halothane death rates exceed those for all the other four agents in only five instances. These were all cases of young females of different risks, as shown in Table 14. Cells B1 and B2 may be disregarded, because they are based on such small numbers; but risks U and A1 should be considered more seriously.

Inspection of Table 6 for nitrous oxide-barbiturate and cyclopropane rates would support the suspicion that halothane might have disadvantages for females, particularly young ones. If this were true and halothane rates for females were outstandingly high, then when we compare the halothane rate with that of any other agent, the ratio of the two rates for females will be larger than the corresponding ratio for males, unless the other agent also produces exceptionally high rates for females. We do not find this to be true when halothane rates are compared with ether rates; here the difference in ratios between the sexes is reversed. The comparison with ether shows that, although ether rates are generally lower than halothane rates, for the risk A1, age 10-49 females listed above, the two rates are very close, the ether rate being 0.00062, compared with the halothane rate of 0.00063 (see Table 6).

Inspection of the other two cells under suspicion shows that the cyclopropane and

TABLE 11.--FITTED DEATH RATES IN LARGE CELLS FOR LOW-DEATH-RATE OPERATIONS, HALOTHANE COMPARED WITH ETHER

Risk level: U = unknown
A1 = risks 1 + 2

Risk	Age	Female		Male	
		H	E	H	E
U	0-9			0.0017 (20)	0.0004 (29)
U	10-49	0.0018 (41)*	0.0010 (15)		
A1	0-9	0.0012 (56)	0.0006 (93)	0.0004 (85)	0.0002 (131)
A1	10-49	0.0006 (256)	0.0006 (98)	0.0005 (107)	0.0004 (37)
A1	50-69	0.0020 (78)	0.0025 (22)	0.0016 (70)	0.0016 (18)

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 12.--SUMMARY OF FITTED DEATH RATES FOR LOW-DEATH-RATE OPERATIONS OVER ALL AGES FOR RISK CATEGORIES B1, A2, and B2, HALOTHANE COMPARED WITH ETHER

Risk level: B1 = risks 3 + 4
A2 = risk 5
B2 = risk 6

Risk	H	E
B1	0.0221 (36)*	0.0172 (12)
A2	0.0011 (26)	0.0078 (3)
B2	0.0349 (7)	0.0445 (11)

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 13.--FITTED DEATH RATES IN LARGE CELLS FOR LOW-DEATH-RATE OPERATIONS, HALOTHANE COMPARED WITH OTHER

Risk level: U = unknown
A1 = risks 1 + 2

Risk	Age	Female		Male	
		H	O	H	O
U	0-9			0.0017 (20)	0.0009 (30)
U	10-49	0.0018 (41)*	0.0022 (17)		
A1	0-9	0.0012 (56)	0.0004 (104)	0.0004 (85)	0.0002 (136)
A1	10-49	0.0006 (256)	0.0006 (109)	0.0005 (107)	0.0005 (39)
A1	50-69	0.0020 (78)	0.0033 (29)	0.0016 (70)	0.0031 (22)

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 14.--CELLS IN WHICH HALOTHANE FITTED DEATH RATES FOR LOW-DEATH-RATE OPERATIONS ARE HIGHER THAN THOSE OF THE OTHER FOUR AGENTS

Risk level: U = unknown
A1 = risks 1 + 2
B1 = risks 3 + 4
B2 = risk 6

Risk	Age	Sex	Halothane rate	Estimated exposed (in hundreds)
U	0-9	f	0.00319	12
A1	0-9	f	0.00116	56
A1	10-49	f	0.00063	256
B1	0-9	f	0.03962	1
B2	0-9	f	0.06336	<1

halothane rates are also very close together. They are:

		C		H	
Risk	Age	Rate	EE	Rate	EE
U	0-9	0.00293	1016	0.00319	1241
A1	0-9	0.00090	3580	0.00116	5568

Thus, in the risk U cell, one more cyclopropane death would make the ratio of the cyclopropane rate to the halothane rate larger than unity, and the same is true for the risk A1 cell. On the basis of indicating a sex difference, and in terms of the actual magnitude of the rates involved, these three cells do not seem to indicate excessive deaths related to halothane. A further comparison supports this conclusion. If halothane caused excessive deaths in age group 0-9, we would expect the rate ratios to be smaller for this age group compared with other age groups, for every agent comparison. They are not.

When halothane is compared with other agents on a cell-by-cell basis, no consistent evidence of excessive deaths from halothane arises in any sector of the population, nor is there any tendency for relatively high halothane rates to be associated with any of the variables considered.

Essentially, we have found that the magnitude of differences in rates between the several agents and halothane is neither large nor very consistent. The impression from Tables 7, 9, and 11 is that for low-death-rate operations halothane did not perform quite as well as nitrous oxide-barbiturate, cyclopropane, or ether. To check this impression, we ranked all the agents except Other from 1 (lowest crude death rate) to 4 (highest crude death rate) for each of the eight (sex, age) groupings within each risk. Then we summed the ranks within each risk. The resulting totals are shown in Table 15.

All told, then, one gets the distinct impression that for the low-death-rate operations, although the differences are small and inconsistent, the order of increasing death rate is ether, nitrous oxide-barbiturate, halothane, and cyclopropane, and that the first two are especially close. Nevertheless, the rates are all small and nearly comparable. It must be emphasized here, as everywhere else in this report, that the rates were obtained from existing patterns of use, and not from the results of a prospective randomized study. And, of course, no account could be taken of why one or another anesthetic may have been especially indicated in an individual operation.

TABLE 15.--SUMMARY OF RANKINGS OF OBSERVED DEATH RATES FOR THE LOW-DEATH-RATE OPERATIONS*

Risk level: U = unknown
A1 = risks 1 + 2
B1 = risks 3 + 4
A2 = risk 5
B2 = risk 6

Risk	H	N-B	C	E	Totals
U	25	13.5	26.5	15	80
A1	22	18	23	17	80
B1	20	19	24.5	16.5	80
A2	21	**19.5	21.5	**18	80
B2	19	**21	26.5	**13.5	80
Totals	107	91	122	80	400

*A score of 1 was assigned to the agent with the lowest crude death rate for each sex-age grouping within each risk, 2 for the next lowest, etc.
**Low scores for nitrous oxide-barbiturate and ether for risks A2 and B2 may be due largely to the lack of use, rather than to good performance.

MIDDLE-DEATH-RATE OPERATIONS

General Usage

For the middle-death-rate operations, it was necessary to fit three-dimensional faces. Two models are fitted on differing variables. Model A included five variables: operation (five categories), risk (four categories), sex (two categories), age (four categories), and agent (5 categories). This gave a total of 800 cells, and spread the data too sparsely, so model B was fitted, in which sex was not considered, reducing the number of cells to 400. We first present results from model A and then some from model B. The basic table for model A is not presented, but the detailed data of model B are given in Table 16. All rates presented are deaths/(deaths + EE).

Because young females were the most suspicious-looking group in the low-death-rate operations, as far as a possibility of excess deaths from halothane was concerned, they were studied again for the middle-death-rate operations. We looked for a tendency, in the comparison of halothane with other agents on a cell-by-cell basis, for halothane to have higher death rates when two cells for young females were compared than when the corresponding cells for males were compared. For the youngest age group this occurred only for operation categories 3, 4, and 5 for nitrous oxide-barbiturate; for cyclopropane it almost always occurred; and for ether it was consistently true. For the next age group, the consistency was less: for nitrous oxide-barbiturate it was again not found for operation categories 1 and 2 (except for risk U); for cyclopropane there was no systematic pattern; and for ether the relationship existed for risk U but not for risks A and B. Again, the fact that risk U (unknown) does not reflect the average pattern of the other risks is surprising. We did not find halothane to be especially disadvantageous for young females in middle-death-rate operation categories 1 and 2, which should most nearly resemble the low-death-rate operations.

Because the suspicion about females did not seem justified, we examined the cells to see where halothane rates were higher than those of the other four agents. This involved 120 comparisons; risk C (moribund), for which the rates were erratic because of few cases, was excluded. If each of the five agents had about the same death rates, random distribution would predict that halothane would get the worst rate in 24 instances. In fact, halothane has the worst fitted rate in only the 11 instances shown in Table 17. All these death rates are based on small numbers of estimated exposed; in all except the first one listed, the number of estimated exposed was less than 150. Because the cells listed are spread among different sexes, ages, and operation groups, the table provides no evidence of any real tendency of halothane rates to be excessive, and suggests chance variation.

To confirm this conclusion, the same procedure of selecting cells where the halothane death rate was higher than for the other four agents was carried out on model B, which omitted the sex variable. The five cells that were selected from the 60 possibilities, again excluding risk C (moribund), are shown in Table 18. Because age 0-9, operation category 5, and all three risks showed up in model A for both sexes, that group still appears here, but the two largest cells listed do not show the same combinations of age, risk, and operation categories as in model A, so this supports the previous conclusion of chance variation.

Rates in Large Cells

Although the full table of rates (Table 16) for model B is large for casual examination, much of its message is contained in the larger cells whose rates are especially stable. Such data are given in Table 19. Cyclopropane has a somewhat higher death rate than the other four agents, Other is second highest, halothane and nitrous oxide-barbiturate are nearly equal, and ether may have a slightly lower rate.

Ranking Analysis of Death Rates for the Four Anesthetics

As in the analysis of the low-death-rate operations, another sort of summary statistic can be had by ranking halothane, nitrous oxide-barbiturate, cyclopropane, and ether in ascending order of crude death rates within a cell

TABLE 16.--OBSERVED RATES AND RATES FITTED TO 4 VARIABLES: AGENT, RISK, AGE, AND OPERATION CATEGORY, MIDDLE-DEATH-RATE OPERATIONS, MODEL B

OPERATION CATEGORY 1 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.00308	0.	0.00319	0.00219	0.00481
FIT DEAD	5.1	0.6	3.2	1.8	5.3
FIT EE	1563.3	250.1	910.5	762.3	1431.9
FIT RATE	0.00323	0.00239	0.00349	0.00236	0.00371
RISK U,AGE 10-49					
OBS RATE	0.00119	0.00260	0.00257	0.00263	0.00117
FIT DEAD	13.7	11.0	10.8	3.8	5.7
FIT EE	7463.9	6627.1	3899.5	1960.3	3309.8
FIT RATE	0.00183	0.00166	0.00276	0.00192	0.00173
RISK U,AGE 50-69					
OBS RATE	0.00494	0.00294	0.01100	0.00470	0.00496
FIT DEAD	20.4	13.3	10.6	7.6	10.1
FIT EE	4349.0	3154.9	1337.4	1296.3	1972.1
FIT RATE	0.00467	0.00420	0.00790	0.00580	0.00510
RISK U,AGE 70+					
OBS RATE	0.02073	0.01442	0.03416	0.04542	0.04671
FIT DEAD	19.9	14.1	15.3	10.9	14.8
FIT EE	1033.6	749.8	362.7	287.7	464.9
FIT RATE	0.01885	0.01846	0.04058	0.03634	0.03095
RISK A,AGE 0- 9					
OBS RATE	0.00162	0.00133	0.00149	0.00167	0.00196
FIT DEAD	11.7	3.5	3.5	4.7	10.5
FIT EE	7798.3	1498.0	2016.9	3613.1	5290.9
FIT RATE	0.00150	0.00236	0.00173	0.00130	0.00199
RISK A,AGE 10-49					
OBS RATE	0.00095	0.00071	0.00136	0.00060	0.00138
FIT DEAD	39.0	28.4	32.8	7.9	20.8
FIT EE	46552.2	35053.6	22714.2	11488.5	16091.1
FIT RATE	0.00084	0.00081	0.00144	0.00069	0.00129
RISK A,AGE 50-69					
OBS RATE	0.00409	0.00334	0.00453	0.00210	0.00528
FIT DEAD	72.4	42.9	33.4	11.7	37.7
FIT EE	18202.6	13125.5	7208.8	4337.1	6954.9
FIT RATE	0.00396	0.00325	0.00461	0.00270	0.00538
RISK A,AGE 70+					
OBS RATE	0.01275	0.01694	0.02809	0.02265	0.01885
FIT DEAD	42.9	34.2	26.3	11.6	26.0
FIT EE	2730.4	2373.7	1018.0	588.1	1114.3
FIT RATE	0.01546	0.01421	0.02517	0.01935	0.02283

OPERATION CATEGORY 1 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.03568	0.21109	0.04974	0.03782	0.03369
FIT DEAD	15.3	4.9	4.8	8.9	21.1
FIT EE	357.4	104.0	125.3	326.2	391.4
FIT RATE	0.04103	0.04462	0.03687	0.02662	0.05121
RISK B,AGE 10-49					
OBS RATE	0.01644	0.01836	0.02370	0.02080	0.01629
FIT DEAD	22.6	22.0	28.6	6.3	17.6
FIT EE	1483.6	1194.4	1145.2	300.0	939.5
FIT RATE	0.01500	0.01807	0.02435	0.02058	0.01834
RISK B,AGE 50-69					
OBS RATE	0.03047	0.02940	0.04439	0.02493	0.06935
FIT DEAD	60.9	47.5	39.7	13.4	52.4
FIT EE	1799.9	1503.1	818.9	572.1	944.1
FIT RATE	0.03275	0.03066	0.04627	0.02295	0.05255
RISK B,AGE 70+					
OBS RATE	0.07211	0.06080	0.09238	0.05447	0.09857
FIT DEAD	49.2	53.6	40.9	24.3	48.9
FIT EE	721.4	752.9	396.3	334.5	498.1
FIT RATE	0.06383	0.06649	0.09353	0.06784	0.08947
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	0.06104	0.	0.03518
FIT DEAD	0.9	0.	0.5	0.6	1.0
FIT EE	13.4	0.	9.5	0.	19.9
FIT RATE	0.06423	0.	0.05149	1.00000	0.04856
RISK C,AGE 10-49					
OBS RATE	0.13072	0.	0.56523	0.08134	0.39395
FIT DEAD	3.7	1.6	7.8	1.0	3.9
FIT EE	11.8	23.7	12.9	4.4	18.5
FIT RATE	0.23767	0.06419	0.37584	0.18159	0.17563
RISK C,AGE 50-69					
OBS RATE	0.10916	0.23724	0.29001	1.00000	0.42742
FIT DEAD	4.3	2.3	9.2	1.3	5.9
FIT EE	10.9	14.8	17.3	0.	24.3
FIT RATE	0.28379	0.13520	0.34854	1.00000	0.19503
RISK C,AGE 70+					
OBS RATE	1.00000	0.28059	0.55229	1.00000	0.11471
FIT DEAD	5.1	3.1	13.5	2.2	7.2
FIT EE	1.7	13.4	15.9	6.9	39.6
FIT RATE	0.74719	0.18600	0.45792	0.24170	0.15343

Table 16 (Cont'd)

OPERATION CATEGORY 2 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.00435	0.02115	0.02933	0.	0.01023
FIT DEAD	4.5	0.3	1.8	0.3	5.1
FIT EE	456.5	95.9	72.8	82.3	745.5
FIT RATE	0.00978	0.00327	0.02402	0.00391	0.00677
RISK U,AGE 10-49					
OBS RATE	0.01587	0.00842	0.00260	0.	0.01214
FIT DEAD	15.8	11.9	3.9	0.6	8.8
FIT EE	1274.8	1149.2	355.7	182.0	833.2
FIT RATE	0.01225	0.01027	0.01076	0.00343	0.01043
RISK U,AGE 50-69					
OBS RATE	0.02090	0.01932	0.04556	0.00802	0.01956
FIT DEAD	27.6	19.9	11.5	3.9	16.0
FIT EE	1218.5	1171.3	256.0	206.2	807.5
FIT RATE	0.02218	0.01673	0.04293	0.01865	0.01945
RISK U,AGE 70+					
OBS RATE	0.04876	0.02079	0.07783	0.03012	0.02981
FIT DEAD	18.1	12.8	9.9	2.1	20.1
FIT EE	456.9	560.0	168.2	134.9	413.4
FIT RATE	0.03800	0.02242	0.05536	0.01561	0.04639
RISK A,AGE 0- 9					
OBS RATE	0.00460	0.00604	0.01424	0.00968	0.00667
FIT DEAD	8.9	2.3	2.4	3.5	10.0
FIT EE	1517.2	340.5	138.7	530.0	1492.4
FIT RATE	0.00580	0.00667	0.01680	0.00653	0.00665
RISK A,AGE 10-49					
OBS RATE	0.00465	0.00601	0.00472	0.00136	0.00861
FIT DEAD	22.3	21.9	8.2	3.2	18.4
FIT EE	5179.0	3523.0	1741.3	1417.3	2145.5
FIT RATE	0.00429	0.00619	0.00470	0.00222	0.00851
RISK A,AGE 50-69					
OBS RATE	0.01211	0.01267	0.01863	0.00955	0.01731
FIT DEAD	59.3	56.0	30.8	17.8	42.1
FIT EE	5097.7	4333.4	1779.2	1406.6	2314.5
FIT RATE	0.01149	0.01276	0.01702	0.01251	0.01787
RISK A,AGE 70+					
OBS RATE	0.02580	0.02602	0.02957	0.02915	0.05501
FIT DEAD	33.6	38.8	20.6	9.6	35.5
FIT EE	1087.4	1421.0	548.7	506.7	725.9
FIT RATE	0.02996	0.02656	0.03620	0.01852	0.04661

OPERATION CATEGORY 2 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.06960	0.01799	0.11309	0.07082	0.04016
FIT DEAD	25.3	3.4	5.0	6.8	18.5
FIT EE	412.3	103.1	40.2	113.9	388.1
FIT RATE	0.05792	0.03192	0.11059	0.05609	0.04543
RISK B,AGE 10-49					
OBS RATE	0.09087	0.09215	0.08338	0.09744	0.11749
FIT DEAD	50.8	33.1	19.8	4.6	25.8
FIT EE	514.6	275.2	215.1	46.3	231.5
FIT RATE	0.08981	0.10722	0.08419	0.09057	0.10013
RISK B,AGE 50-69					
OBS RATE	0.06401	0.06774	0.11046	0.11445	0.07873
FIT DEAD	73.1	45.1	37.7	14.0	36.1
FIT EE	979.1	708.9	308.5	144.7	361.8
FIT RATE	0.06951	0.05975	0.10885	0.08823	0.09080
RISK B,AGE 70+					
OBS RATE	0.09964	0.06898	0.09667	0.03352	0.11918
FIT DEAD	55.7	43.5	32.5	13.6	40.6
FIT EE	525.9	606.8	307.3	211.9	352.2
FIT RATE	0.09585	0.06688	0.09576	0.06030	0.10347
RISK C,AGE 0- 9					
OBS RATE	0.27180	0.	0.	1.00000	1.00000
FIT DEAD	2.3	0.	0.8	1.4	2.5
FIT EE	4.9	0.	0.0	0.	0.4
FIT RATE	0.31864	0.	0.95264	1.00000	0.84684
RISK C,AGE 10-49					
OBS RATE	0.10983	1.00000	1.00000	1.00000	0.
FIT DEAD	3.1	1.1	2.1	0.6	4.0
FIT EE	35.5	1.4	0.9	0.	2.8
FIT RATE	0.08092	0.44045	0.69929	1.00000	0.58894
RISK C,AGE 50-69					
OBS RATE	0.11053	1.00000	0.43821	1.00000	1.00000
FIT DEAD	4.0	2.0	7.0	2.3	5.7
FIT EE	33.4	1.2	1.6	0.	3.7
FIT RATE	0.10591	0.63197	0.81450	1.00000	0.60494
RISK C,AGE 70+					
OBS RATE	0.34212	0.34851	1.00000	1.00000	0.33324
FIT DEAD	5.6	2.9	11.0	2.7	10.8
FIT EE	11.9	3.0	5.1	0.	19.0
FIT RATE	0.32051	0.48782	0.68168	1.00000	0.36148

Table 16 (Cont'd)

OPERATION CATEGORY 3 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.02025	0.	0.11063	0.	0.02602
FIT DEAD	1.7	0.1	2.5	0.4	2.3
FIT EE	65.3	4.8	47.7	39.0	54.4
FIT RATE	0.02499	0.01282	0.05000	0.01096	0.04103
RISK U,AGE 10-49					
OBS RATE	0.01311	0.00823	0.01294	0.00708	0.02922
FIT DEAD	6.9	4.2	5.7	1.0	3.3
FIT EE	544.5	433.2	337.3	186.3	161.2
FIT RATE	0.01243	0.00951	0.01662	0.00511	0.02029
RISK U,AGE 50-69					
OBS RATE	0.02569	0.02120	0.03920	0.03379	0.04448
FIT DEAD	22.8	11.7	23.1	14.5	11.9
FIT EE	1021.3	490.8	525.7	351.5	259.9
FIT RATE	0.02180	0.02326	0.04203	0.03972	0.04389
RISK U,AGE 70+					
OBS RATE	0.05450	0.09160	0.09706	0.12852	0.16300
FIT DEAD	16.7	10.1	29.7	11.1	17.4
FIT EE	262.3	134.0	240.1	82.2	77.4
FIT RATE	0.05990	0.07001	0.11010	0.11880	0.18365
RISK A,AGE 0- 9					
OBS RATE	0.00817	0.	0.02433	0.01174	0.00766
FIT DEAD	3.4	0.4	2.2	1.7	4.3
FIT EE	352.0	35.9	107.2	285.0	441.2
FIT RATE	0.00948	0.01141	0.02048	0.00600	0.00954
RISK A,AGE 10-49					
OBS RATE	0.00605	0.00650	0.00866	0.00237	0.00804
FIT DEAD	16.3	11.6	13.5	2.9	10.7
FIT EE	2643.4	2077.7	1435.0	1213.5	1239.5
FIT RATE	0.00612	0.00556	0.00929	0.00241	0.00857
RISK A,AGE 50-69					
OBS RATE	0.01881	0.02004	0.02573	0.02795	0.02596
FIT DEAD	60.3	36.6	50.4	29.5	35.2
FIT EE	3040.5	1691.5	1891.2	1194.2	1324.5
FIT RATE	0.01945	0.02117	0.02596	0.02410	0.02589
RISK A,AGE 70+					
OBS RATE	0.04408	0.04511	0.05759	0.03702	0.08407
FIT DEAD	31.0	27.4	40.9	17.9	27.8
FIT EE	750.5	535.3	684.8	259.9	408.1
FIT RATE	0.03971	0.04867	0.05632	0.06429	0.06386

OPERATION CATEGORY 3 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	1.00000	1.00000	0.05422	0.01582	0.19713
FIT DEAD	4.9	0.5	3.3	2.0	7.3
FIT EE	43.8	9.6	24.3	46.4	130.0
FIT RATE	0.10152	0.05196	0.11879	0.04101	0.05294
RISK B,AGE 10-49					
OBS RATE	0.15955	0.05699	0.07837	0.10870	0.16887
FIT DEAD	18.3	14.3	21.6	2.4	13.3
FIT EE	133.5	158.6	154.0	33.4	168.2
FIT RATE	0.12065	0.08293	0.12293	0.06841	0.07337
RISK B,AGE 50-69					
OBS RATE	0.08414	0.06851	0.11045	0.09109	0.06478
FIT DEAD	63.9	41.9	71.5	23.0	46.7
FIT EE	676.0	615.7	648.8	235.3	593.1
FIT RATE	0.08638	0.06369	0.09927	0.08912	0.07297
RISK B,AGE 70+					
OBS RATE	0.14469	0.16646	0.18978	0.37146	0.11998
FIT DEAD	51.8	51.2	87.6	29.5	57.7
FIT EE	235.9	285.5	426.0	116.8	318.4
FIT RATE	0.18010	0.15219	0.17065	0.20183	0.15349
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	1.00000	0.	1.00000
FIT DEAD	1.0	0.	2.0	0.9	2.2
FIT EE	0.	0.	0.	0.	0.
FIT RATE	1.00000	0.	1.00000	1.00000	1.00000
RISK C,AGE 10-49					
OBS RATE	1.00000	0.10358	1.00000	0.01323	0.12934
FIT DEAD	2.5	2.9	8.3	0.7	4.6
FIT EE	9.5	31.7	11.7	61.7	8.1
FIT RATE	0.21110	0.08337	0.41422	0.01068	0.36300
RISK C,AGE 50-69					
OBS RATE	0.10505	0.07257	0.24752	1.00000	0.22905
FIT DEAD	2.0	2.8	12.0	1.9	4.2
FIT EE	15.8	26.3	39.7	0.	16.2
FIT RATE	0.11171	0.09766	0.23267	1.00000	0.20565
RISK C,AGE 70+					
OBS RATE	1.00000	1.00000	0.46715	1.00000	1.00000
FIT DEAD	2.5	4.3	21.8	2.5	7.0
FIT EE	0.2	2.2	4.9	12.9	2.6
FIT RATE	0.91962	0.66217	0.81631	0.16281	0.72697

Table 16 (Cont'd)

OPERATION CATEGORY 4 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.05311	0.06844	0.11333	0.09532	0.06696
FIT DEAD	27.9	1.6	22.2	6.8	29.5
FIT EE	504.5	40.3	220.7	171.9	227.9
FIT RATE	0.05248	0.03844	0.09124	0.03785	0.11472
RISK U,AGE 10-49					
OBS RATE	0.04649	0.04252	0.03843	0.00349	0.09686
FIT DEAD	38.0	23.7	11.2	3.8	15.2
FIT EE	971.0	501.9	293.0	416.4	195.2
FIT RATE	0.03765	0.04516	0.03691	0.00913	0.07235
RISK U,AGE 50-69					
OBS RATE	0.04940	0.05961	0.07128	0.05018	0.14595
FIT DEAD	63.1	41.3	30.1	24.2	31.4
FIT EE	1142.7	547.7	339.2	609.9	285.4
FIT RATE	0.05231	0.07006	0.08139	0.03818	0.09913
RISK U,AGE 70+					
OBS RATE	0.08907	0.13902	0.12375	0.09045	0.23311
FIT DEAD	46.0	30.4	23.6	14.2	41.8
FIT EE	383.0	280.5	157.1	117.7	130.1
FIT RATE	0.10721	0.09773	0.13062	0.10748	0.24338
RISK A,AGE 0- 9					
OBS RATE	0.01999	0.03321	0.04447	0.02441	0.02771
FIT DEAD	27.4	4.8	16.7	13.5	26.8
FIT EE	1329.7	184.3	364.9	410.4	967.9
FIT RATE	0.02018	0.02522	0.04365	0.03178	0.02692
RISK A,AGE 10-49					
OBS RATE	0.01019	0.01086	0.01325	0.00473	0.01534
FIT DEAD	60.2	40.0	30.6	8.1	33.2
FIT EE	5759.7	3643.2	2292.4	2212.8	1963.8
FIT RATE	0.01034	0.01086	0.01316	0.00362	0.01662
RISK A,AGE 50-69					
OBS RATE	0.02674	0.03421	0.03775	0.02181	0.03930
FIT DEAD	108.1	75.6	73.5	32.6	61.1
FIT EE	3510.4	2413.4	1895.4	1428.1	1607.2
FIT RATE	0.02988	0.03039	0.03731	0.02234	0.03662
RISK A,AGE 70+					
OBS RATE	0.08244	0.03832	0.06670	0.09717	0.07036
FIT DEAD	61.3	53.6	40.3	16.8	49.0
FIT EE	874.0	1107.0	538.0	198.1	585.9
FIT RATE	0.06555	0.04618	0.06970	0.07830	0.07711

OPERATION CATEGORY 4 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.13082	0.11488	0.18745	0.13580	0.16309
FIT DEAD	106.6	16.6	54.7	44.1	97.0
FIT EE	674.0	114.3	218.1	253.4	589.4
FIT RATE	0.13657	0.12695	0.20047	0.14817	0.14137
RISK B,AGE 10-49					
OBS RATE	0.07972	0.14229	0.11900	0.05911	0.08460
FIT DEAD	113.3	85.9	69.6	12.0	55.3
FIT EE	1126.7	615.3	617.1	219.3	523.9
FIT RATE	0.09134	0.12247	0.10132	0.05207	0.09542
RISK B,AGE 50-69					
OBS RATE	0.13496	0.11927	0.14117	0.07933	0.11686
FIT DEAD	163.0	128.1	125.8	38.8	92.2
FIT EE	1290.6	829.9	696.4	433.1	603.9
FIT RATE	0.11215	0.13373	0.15301	0.08218	0.13250
RISK B,AGE 70+					
OBS RATE	0.16977	0.15793	0.17085	0.15436	0.19480
FIT DEAD	124.1	126.4	88.9	36.1	98.5
FIT EE	558.7	686.1	440.9	168.6	471.8
FIT RATE	0.18173	0.15556	0.16785	0.17638	0.17268
RISK C,AGE 0- 9					
OBS RATE	0.20301	0.	0.31125	1.00000	0.78923
FIT DEAD	17.1	0.	16.5	8.7	22.7
FIT EE	55.9	0.	29.6	0.	32.3
FIT RATE	0.23390	0.	0.35817	1.00000	0.41212
RISK C,AGE 10-49					
OBS RATE	0.33651	0.16751	0.51049	0.09859	0.59458
FIT DEAD	25.6	12.4	27.6	3.1	31.3
FIT EE	48.5	35.9	30.4	47.3	27.2
FIT RATE	0.34500	0.25621	0.47591	0.06088	0.53533
RISK C,AGE 50-69					
OBS RATE	0.35240	0.40982	0.33364	1.00000	0.25298
FIT DEAD	19.8	15.0	52.7	7.4	32.3
FIT EE	62.5	35.5	94.7	0.	60.4
FIT RATE	0.24038	0.29705	0.35744	1.00000	0.34827
RISK C,AGE 70+					
OBS RATE	0.47645	1.00000	0.53918	0.08172	0.25890
FIT DEAD	9.6	7.6	23.1	2.9	19.7
FIT EE	3.5	17.7	38.1	25.1	48.6
FIT RATE	0.73078	0.30127	0.37790	0.10352	0.28887

Table 16 (Cont'd)

OPERATION CATEGORY 5 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.26049	0.	0.07664	0.12462	0.07797
FIT DEAD	11.8	0.4	12.3	3.7	6.7
FIT EE	41.8	10.5	85.4	34.9	102.8
FIT RATE	0.22041	0.03765	0.12634	0.09545	0.06153
RISK U,AGE 10-49					
OBS RATE	0.02818	0.08810	0.05885	0.03307	0.03944
FIT DEAD	14.7	7.2	10.4	2.8	4.9
FIT EE	319.0	103.0	245.4	102.0	157.1
FIT RATE	0.04400	0.06510	0.04064	0.02677	0.03046
RISK U,AGE 50-69					
OBS RATE	0.09562	0.16204	0.16724	0.18569	0.07339
FIT DEAD	32.1	25.8	38.8	16.8	17.5
FIT EE	342.6	89.5	169.9	127.4	174.0
FIT RATE	0.08573	0.22394	0.18570	0.11628	0.09159
RISK U,AGE 70+					
OBS RATE	0.17223	0.33170	0.34100	0.09199	0.19607
FIT DEAD	19.4	10.6	28.5	8.8	14.8
FIT EE	116.6	15.7	91.2	43.5	70.4
FIT RATE	0.14255	0.40293	0.23806	0.16736	0.17369
RISK A,AGE 0- 9					
OBS RATE	0.11493	0.02126	0.06830	0.05487	0.04293
FIT DEAD	13.7	1.0	9.2	9.6	10.5
FIT EE	103.7	68.7	139.6	132.1	207.7
FIT RATE	0.11644	0.01417	0.06202	0.06787	0.04793
RISK A,AGE 10-49					
OBS RATE	0.02302	0.01956	0.02554	0.01841	0.04221
FIT DEAD	28.2	10.1	28.9	7.9	18.9
FIT EE	1026.1	615.4	1094.1	495.0	432.9
FIT RATE	0.02673	0.01609	0.02575	0.01576	0.04183
RISK A,AGE 50-69					
OBS RATE	0.04355	0.03595	0.06269	0.03890	0.07329
FIT DEAD	48.9	28.9	70.9	22.3	43.9
FIT EE	1154.4	656.6	1094.0	551.1	542.9
FIT RATE	0.04065	0.04216	0.06090	0.03891	0.07489
RISK A,AGE 70+					
OBS RATE	0.06627	0.14561	0.12603	0.06790	0.29201
FIT DEAD	18.2	9.0	28.9	8.1	17.7
FIT EE	184.0	65.0	226.9	85.4	110.8
FIT RATE	0.09006	0.12221	0.11306	0.08708	0.13773

OPERATION CATEGORY 5 MIDDLE DEATH-RATE OPERATIONS

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.42061	0.03471	0.19295	0.12729	0.11113
FIT DEAD	24.8	2.6	20.3	21.3	26.1
FIT EE	48.2	50.2	91.1	139.6	221.1
FIT RATE	0.33968	0.04921	0.18193	0.13214	0.10555
RISK B,AGE 10-49					
OBS RATE	0.14578	0.11074	0.15628	0.07199	0.11527
FIT DEAD	48.1	31.7	85.5	15.6	42.1
FIT EE	306.2	203.9	534.8	139.8	335.8
FIT RATE	0.13564	0.13471	0.13782	0.10030	0.11141
RISK B,AGE 50-69					
OBS RATE	0.09869	0.18473	0.19170	0.08001	0.15628
FIT DEAD	84.0	90.4	198.3	43.8	111.6
FIT EE	696.2	476.4	784.7	511.9	637.8
FIT RATE	0.10764	0.15951	0.20171	0.07874	0.14890
RISK B,AGE 70+					
OBS RATE	0.26879	0.46401	0.24527	0.22307	0.17358
FIT DEAD	47.2	44.2	117.0	32.4	67.2
FIT EE	168.4	74.2	316.9	194.3	243.4
FIT RATE	0.21872	0.37371	0.26964	0.14292	0.21639
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	1.00000	1.00000	0.26880
FIT DEAD	6.7	0.	5.2	4.5	6.7
FIT EE	5.8	0.	13.9	0.	4.8
FIT RATE	0.53838	0.	0.27147	1.00000	0.58076
RISK C,AGE 10-49					
OBS RATE	0.16279	0.39395	0.14802	1.00000	0.35266
FIT DEAD	16.1	6.0	25.2	3.7	23.1
FIT EE	84.0	45.5	131.1	0.	30.8
FIT RATE	0.16067	0.11662	0.16116	1.00000	0.42800
RISK C,AGE 50-69					
OBS RATE	0.16743	0.21619	0.27172	1.00000	0.48576
FIT DEAD	14.0	12.9	57.0	7.2	34.9
FIT EE	69.1	25.1	171.0	0.	36.4
FIT RATE	0.16813	0.33901	0.25013	1.00000	0.49005
RISK C,AGE 70+					
OBS RATE	0.71890	0.32674	0.37869	1.00000	1.00000
FIT DEAD	17.2	11.1	71.6	7.7	41.3
FIT EE	5.4	5.8	108.1	0.	35.2
FIT RATE	0.76094	0.65725	0.39867	1.00000	0.53992

TABLE 17.--CELLS IN WHICH HALOTHANE DEATH RATES ARE HIGHER THAN THOSE OF THE OTHER FOUR AGENTS, MIDDLE-DEATH-RATE OPERATIONS, MODEL A,* RISK C EXCLUDED

Operation category	Risk	Age	Sex	Rate	Estimated exposed
2	U	10-49	m	0.0108	714
3	B	0-9	f	0.1334	14
3	B	10-49	f	0.1208	68
3	B	70 +	f	0.1826	107
5	U	0-9	m	0.2329	20
5	U	0-9	f	0.2066	21
5	A	0-9	m	0.1484	41
5	A	0-9	f	0.0944	63
5	B	0-9	f	0.4112	19
5	B	0-9	m	0.2852	30
5	B	10-49	f	0.1215	142

*Basic table for model A is not presented.

TABLE 18.--CELLS IN WHICH HALOTHANE HAD THE HIGHEST DEATH RATE IN THE MODEL B ANALYSIS OF MIDDLE-DEATH-RATE OPERATIONS, RISK C EXCLUDED

Operation category	Risk	Age	Rate	Estimated exposed halothane (hundreds)
2	U	10-49	0.012	13
4	B	70 +	0.182	56
5	U	0-9	0.220	*0
5	A	0-9	0.116	1
5	B	0-9	0.340	**0

*42 estimated exposed.
**48 estimated exposed.

TABLE 19.--FITTED DEATH RATES FOR CELLS IN WHICH AT LEAST ONE AGENT HAS AT LEAST 2500 ESTIMATED EXPOSED, MIDDLE-DEATH-RATE OPERATIONS, MODEL B

Operation category 1

Risk	Age	H	N-B	C	E	O
U	10-49	0.0018 (75)*	0.0017 (66)	0.0028 (39)	0.0019 (20)	0.0017 (33)
U	50-69	0.0047 (44)	0.0042 (32)	0.0079 (13)	0.0058 (13)	0.0051 (20)
A	0-9	0.0015 (78)	0.0024 (15)	0.0017 (20)	0.0013 (36)	0.0020 (53)
A	10-49	0.0008 (466)	0.0008 (351)	0.0014 (227)	0.0007 (115)	0.0013 (161)
A	50-69	0.0040 (182)	0.0033 (131)	0.0046 (72)	0.0027 (43)	0.0054 (70)
A	70 +	0.0155 (27)	0.0142 (24)	0.0252 (10)	0.0194 (6)	0.0228 (11)

Operation category 2

Risk	Age	H	N-B	C	E	O
A	10-49	0.0043 (52)	0.0062 (35)	0.0047 (17)	0.0022 (14)	0.0085 (21)
A	50-69	0.0115 (51)	0.0128 (43)	0.0170 (18)	0.0125 (14)	0.0179 (23)

Operation category 3

Risk	Age	H	N-B	C	E	O
A	10-49	0.0061 (26)	0.0056 (21)	0.0093 (14)	0.0024 (12)	0.0086 (12)
A	50-69	0.0194 (30)	0.0212 (17)	0.0260 (19)	0.0241 (12)	0.0259 (13)

Operation category 4

Risk	Age	H	N-B	C	E	O
A	10-49	0.0103 (58)	0.0109 (36)	0.0132 (23)	0.0036 (22)	0.0166 (20)
A	50-69	0.0299 (35)	0.0304 (24)	0.0373 (19)	0.0223 (14)	0.0366 (16)

*Numbers in parentheses are estimated exposed in hundreds.

(fixed risk, age, and operation category). This ranking was done and then summed over ages to give the summaries in Table 20 (low totals imply low death rates). As before, we did not include agent 5 (Other) in the comparison. The summed rankings are fairly consistent from one risk level to another within an operation category, and from one operation category to another. Recall

TABLE 20.--AGENT RANKS TOTALED OVER AGES FOR EACH RISK CATEGORY WITHIN OPERATION CATEGORY, MIDDLE-DEATH-RATE OPERATIONS, MODEL B

Operation category 1

Risk	H	N-B	C	E	Total
U	9	6	13	12	40
A	10	7	14	9	40
B	8	10	15	7	40
Total	27	23	42	28	120

Operation category 2

U	12	9	14	5	40
A	6	11	15	8	40
B	9	8	11	12	40
Total	27	28	40	25	120

Operation category 3

U	7	5	10	8	*30
A	5	8	11	6	*30
B	7	4	9	10	*30
Total	19	17	30	24	90

Operation category 4

U	7	12	13	8	40
A	8	10	14	8	40
B	8	10	15	7	40
Total	23	32	42	23	120

Operation category 5

U	4	9	10	7	*30
A	11	8	14	7	40
B	8	9	10	3	*30
Total	23	26	34	17	100

Grand summary

Operation category	H	N-B	C	E	Total
1	27	23	42	28	120
2	27	28	40	25	120
3	19	17	30	24	90
4	23	32	42	23	120
5	23	26	34	17	100
Total	119	126	188	117	550

*Subtotals come to 40 unless some age group had few cases.

that crude rates are preferred to fitted rates to get a notion of the consistency of the ordering in the face of the variability of the data.

The implication of these tables is that for the middle-death-rate operations, cyclopropane's death rates are consistently higher than those of the other three agents. The others, in turn, are roughly equal as measured by ranks.

Discussion

There were differences between ages in the relative death rates of the agents and in the usage patterns. No one agent always had higher rates than the others, but for the first three risk categories, cyclopropane death rates were higher than those of halothane, nitrous oxide-barbiturate, and ether. Cyclopropane's rate was much the same as that for agent 5 (Other). As always, we must be wary of concluding that the same results would hold in an experiment, and we must not attribute the death rates themselves to the anesthetic. The difference between death rates for anesthetics is as close as we can hope to come to assigning cause in such an investigation.

CHOLECYSTECTOMIES

Table 21 displays smoothed death rates by agent, sex, risk, and age for each of three operation codes:

- code 40: cholecystectomy alone,
- code 41: cholecystectomy and/or bile duct, and
- code 42: cholecystectomy and/or bile duct, and other major procedures.

In fitting these rates, we used the two-factor effects for all pairs of the five variables except sex × operation code, sex × risk, and sex × age. Inasmuch as about 60 percent of patients having cholecystectomies fall into categories risk A (1+2+5), and age 0-49 or 50-69, a general idea of the data can be had from a shorter table, Table 22.

Tables 21 and 22 show that death rates for males were about twice those for females for corresponding operation, agent, risk, and age group. When anesthetics are compared, halothane looks relatively better for the older of the two age groups. Considering the sizes of the samples, a visual analysis of Table 22 leaves little basis

TABLE 21.--OBSERVED RATES AND RATES FITTED TO 5 VARIABLES: AGENT, SEX, RISK, AGE, AND OPERATION CODE

OPERATION CODE 40 — CHOLECYSTECTOMY RATES

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
	FEMALE					MALE				
RISK U,AGE 0-49										
OBS RATE	0.00466	0.	0.	0.	0.	0.	0.	0.01285	0.	0.
FIT DEAD	0.2	0.1	0.2	0.1	0.3	0.2	0.1	0.2	0.1	0.2
FIT EE	182.7	171.1	147.5	80.2	35.1	87.3	56.8	79.2	38.3	13.1
FIT RATE	0.00097	0.00069	0.00110	0.00073	0.00711	0.00188	0.00134	0.00224	0.00202	0.01744
RISK U,AGE 50-69										
OBS RATE	0.01026	0.	0.01063	0.	0.03303	0.01582	0.	0.	0.	0.03981
FIT DEAD	0.7	0.2	0.9	0.3	0.7	0.6	0.2	1.0	0.4	0.6
FIT EE	220.4	124.4	136.9	70.2	34.4	105.2	41.3	73.5	33.5	12.9
FIT RATE	0.00296	0.00198	0.00636	0.00468	0.01904	0.00570	0.00383	0.01283	0.01287	0.04588
RISK U,AGE 70+										
OBS RATE	0.01421	0.	1.00000	0.00666	0.	0.	0.04317	1.00000	1.00000	0.28765
FIT DEAD	1.2	0.6	1.8	0.7	1.6	1.1	0.4	2.0	1.0	1.5
FIT EE	64.5	31.1	38.8	20.4	14.0	30.8	10.3	20.8	9.7	5.2
FIT RATE	0.01806	0.02037	0.04466	0.03444	0.10419	0.03430	0.03884	0.08671	0.09007	0.22372
RISK A,AGE 0-49										
OBS RATE	0.	0.00137	0.00086	0.	0.	0.	0.	0.	0.00995	0.03153
FIT DEAD	0.4	0.5	0.3	0.2	0.6	0.4	0.3	0.4	0.2	0.6
FIT EE	822.8	715.4	971.0	417.1	340.2	392.8	237.5	521.6	199.1	127.0
FIT RATE	0.00054	0.00071	0.00036	0.00037	0.00175	0.00104	0.00138	0.00073	0.00103	0.00433
RISK A,AGE 50-69										
OBS RATE	0.	0.00852	0.00305	0.00262	0.	0.00440	0.00366	0.01345	0.	0.00522
FIT DEAD	2.7	1.7	3.1	1.4	2.6	2.5	1.1	3.4	1.9	2.4
FIT EE	962.9	504.9	874.2	354.4	323.4	459.8	167.6	469.6	169.1	120.8
FIT RATE	0.00280	0.00345	0.00352	0.00405	0.00802	0.00539	0.00667	0.00712	0.01117	0.01964
RISK A,AGE 70+										
OBS RATE	0.02680	0.03225	0.07148	0.03943	0.03932	0.07226	0.01479	0.05376	0.01958	0.05322
FIT DEAD	2.7	2.5	3.5	1.7	3.5	2.5	1.6	3.8	2.3	3.2
FIT EE	201.6	90.3	177.4	73.6	94.0	96.3	30.0	95.3	35.1	35.1
FIT RATE	0.01307	0.02690	0.01927	0.02298	0.03557	0.02494	0.05098	0.03837	0.06128	0.08374
RISK B,AGE 0-49										
OBS RATE	0.	0.06104	0.	0.	0.	0.	0.07257	0.	0.05747	0.10981
FIT DEAD	0.6	0.6	0.6	0.2	1.0	0.5	0.4	0.6	0.2	0.9
FIT EE	43.4	38.9	91.1	30.9	43.2	20.7	12.9	48.9	14.8	16.1
FIT RATE	0.01256	0.01609	0.00626	0.00516	0.02200	0.02398	0.03080	0.01263	0.01420	0.05280
RISK B,AGE 50-69										
OBS RATE	0.00918	0.	0.04676	0.04067	0.03148	0.05185	0.	0.01173	0.02210	0.09529
FIT DEAD	2.2	1.5	3.4	1.0	2.8	2.1	0.9	3.7	1.3	2.6
FIT EE	128.4	69.3	207.1	66.4	103.6	61.3	23.0	111.3	31.7	38.7
FIT RATE	0.01714	0.02057	0.01613	0.01484	0.02668	0.03258	0.03921	0.03221	0.04013	0.06359
RISK B,AGE 70+										
OBS RATE	0.04398	0.16449	0.04644	1.00000	0.06584	0.02359	1.00000	0.12922	0.04798	0.15419
FIT DEAD	3.9	3.7	6.8	2.1	6.7	3.6	2.4	7.4	2.8	6.2
FIT EE	72.3	33.3	113.1	37.1	81.1	34.5	11.1	60.8	17.7	30.3
FIT RATE	0.05161	0.09997	0.05685	0.05442	0.07638	0.09511	0.17751	0.10907	0.13772	0.17006

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Table 21 (Cont'd)

OPERATION CODE 41 — CHOLECYSTECTOMY RATES

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
			FEMALE					MALE		
RISK U,AGE 0-49										
OBS RATE	0.	0.	0.05070	0.	0.	0.	0.01803	0.	0.	0.05370
FIT DEAD	0.4	0.3	0.3	0.1	0.3	0.3	0.2	0.3	0.1	0.2
FIT EE	68.3	72.8	38.4	23.7	13.3	32.6	24.2	20.6	11.3	5.0
FIT RATE	0.00545	0.00437	0.00775	0.00397	0.01971	0.01048	0.00845	0.01562	0.01094	0.04745
RISK U,AGE 50-69										
OBS RATE	0.02180	0.04317	0.00992	0.	0.08624	0.	0.	0.12811	0.	0.
FIT DEAD	1.5	0.7	1.7	0.6	0.8	1.3	0.5	1.9	0.7	0.7
FIT EE	95.0	61.1	41.0	23.9	15.0	45.4	20.3	22.0	11.4	5.6
FIT RATE	0.01516	0.01142	0.03998	0.02314	0.04778	0.02888	0.02195	0.07798	0.06169	0.11059
RISK U,AGE 70+										
OBS RATE	0.11864	1.00000	0.04122	1.00000	0.	1.00000	0.21211	0.16805	1.00000	1.00000
FIT DEAD	2.3	1.6	3.1	1.1	1.6	2.1	1.0	3.3	1.4	1.5
FIT EE	62.1	34.1	26.0	15.5	13.6	29.6	11.3	14.0	7.4	5.1
FIT RATE	0.03571	0.04495	0.10558	0.06521	0.10449	0.06674	0.08379	0.19338	0.16220	0.22428
RISK A,AGE 0-49										
OBS RATE	0.00275	0.00738	0.	0.	0.00391	0.00537	0.01678	0.	0.	1.00000
FIT DEAD	0.7	1.0	0.5	0.2	0.5	0.6	0.7	0.5	0.2	0.4
FIT EE	325.3	322.2	267.1	130.2	136.1	155.3	107.0	143.5	62.2	50.8
FIT RATE	0.00213	0.00314	0.00177	0.00142	0.00344	0.00411	0.00609	0.00359	0.00393	0.00847
RISK A,AGE 50-69										
OBS RATE	0.00962	0.00888	0.02118	0.02167	0.	0.02620	0.00936	0.00620	0.06067	0.12844
FIT DEAD	4.5	3.7	4.5	1.8	2.2	4.1	2.4	4.9	2.4	2.0
FIT EE	439.0	262.3	277.3	127.6	149.2	209.6	87.1	148.9	60.9	55.7
FIT RATE	0.01010	0.01393	0.01585	0.01417	0.01443	0.01932	0.02671	0.03167	0.03836	0.03501
RISK A,AGE 70+										
OBS RATE	0.02359	0.01853	0.03220	1.00000	0.03258	0.01617	0.06244	0.04252	0.02297	1.00000
FIT DEAD	3.8	4.6	4.4	1.9	2.5	3.5	3.0	4.8	2.5	2.3
FIT EE	205.4	104.7	125.7	59.2	96.9	98.1	34.8	67.5	28.3	36.2
FIT RATE	0.01833	0.04198	0.03358	0.03121	0.02526	0.03481	0.07847	0.06592	0.08207	0.06034
RISK B,AGE 0-49										
OBS RATE	1.00000	0.	0.	0.	0.10981	1.00000	0.	0.04067	0.	0.
FIT DEAD	1.0	1.4	0.9	0.2	0.8	0.9	0.9	0.9	0.3	0.8
FIT EE	18.8	19.2	27.4	10.6	18.9	9.0	6.4	14.7	5.1	7.1
FIT RATE	0.04826	0.06825	0.03052	0.01970	0.04276	0.08920	0.12460	0.06009	0.05282	0.09965
RISK B,AGE 50-69										
OBS RATE	0.09236	0.15115	0.13613	0.01286	0.18804	0.28059	0.19789	0.30434	0.	0.34998
FIT DEAD	4.1	3.4	5.4	1.4	2.6	3.8	2.2	5.9	1.9	2.4
FIT EE	64.1	39.4	72.0	26.2	52.4	30.6	13.1	38.7	12.5	19.6
FIT RATE	0.06017	0.07976	0.07016	0.05098	0.04774	0.11003	0.14414	0.13288	0.12973	0.11049
RISK B,AGE 70+										
OBS RATE	0.09583	0.14053	0.14208	0.33040	0.07014	0.05636	0.31813	0.08096	1.00000	0.03518
FIT DEAD	6.3	7.5	9.5	2.6	5.4	5.8	4.9	10.3	3.5	5.0
FIT EE	80.7	42.4	87.8	32.7	91.5	38.5	14.1	47.2	15.6	34.2
FIT RATE	0.07194	0.15096	0.09720	0.07375	0.05543	0.13021	0.25678	0.17943	0.18097	0.12694

Table 21 (Cont'd)

OPERATION CODE 42 — CHOLECYSTECTOMY RATES

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
			FEMALE					MALE		
RISK U,AGE 0-49										
OBS RATE	0.05962	0.	0.	0.00923	0.	0.04317	0.	0.	0.	0.01323
FIT DEAD	0.8	0.5	0.7	0.3	0.7	0.8	0.3	0.8	0.4	0.7
FIT EE	84.3	104.2	79.1	63.3	28.4	40.3	34.6	42.5	30.2	10.6
FIT RATE	0.00966	0.00476	0.00882	0.00418	0.02476	0.01849	0.00920	0.01775	0.01151	0.05919
RISK U,AGE 50-69										
OBS RATE	0.01648	0.	0.01971	1.00000	1.00000	0.01323	0.01636	0.14226	0.05090	0.28765
FIT DEAD	2.8	1.0	3.5	1.4	1.8	2.6	0.6	3.9	1.9	1.7
FIT EE	147.0	109.5	106.1	80.1	40.2	70.2	36.4	57.0	38.2	15.0
FIT RATE	0.01892	0.00878	0.03233	0.01726	0.04272	0.03591	0.01692	0.06354	0.04647	0.09957
RISK U,AGE 70+										
OBS RATE	0.02700	0.02977	0.03892	0.	0.09307	0.28765	0.11864	0.20453	1.00000	0.34998
FIT DEAD	3.2	1.6	4.6	1.9	2.7	2.9	1.0	5.0	2.5	2.5
FIT EE	64.7	41.2	45.3	35.0	24.6	30.9	13.7	24.3	16.7	9.2
FIT RATE	0.04701	0.03696	0.09150	0.05213	0.09940	0.08698	0.06940	0.16981	0.13240	0.21474
RISK A,AGE 0-49										
OBS RATE	0.	0.00294	0.00290	0.00357	0.00866	0.01946	0.	0.03030	0.00743	0.00974
FIT DEAD	1.6	1.6	1.1	0.5	1.3	1.4	1.0	1.2	0.7	1.2
FIT EE	243.3	279.3	333.7	211.0	176.2	116.2	92.7	179.2	100.7	65.8
FIT RATE	0.00637	0.00577	0.00340	0.00252	0.00730	0.01223	0.01114	0.00689	0.00696	0.01789
RISK A,AGE 50-69										
OBS RATE	0.01891	0.02272	0.01365	0.02695	0.00380	0.03271	0.15901	0.07598	0.03979	0.05133
FIT DEAD	8.9	5.2	9.5	4.7	5.3	8.2	3.4	10.3	6.2	4.9
FIT EE	411.5	284.9	434.1	259.0	242.1	196.4	94.6	233.2	123.6	90.4
FIT RATE	0.02111	0.01796	0.02134	0.01767	0.02151	0.03999	0.03431	0.04241	0.04754	0.05165
RISK A,AGE 70+										
OBS RATE	0.03460	0.05895	0.05999	0.04191	0.07955	0.06529	0.12881	0.02400	0.16362	0.06840
FIT DEAD	5.5	4.6	6.6	3.5	4.4	5.0	3.0	7.2	4.6	4.1
FIT EE	129.8	76.7	132.7	81.0	106.0	62.0	25.5	71.3	38.7	39.6
FIT RATE	0.04031	0.05689	0.04766	0.04111	0.03973	0.07503	0.10492	0.09226	0.10633	0.09299
RISK B,AGE 0-49										
OBS RATE	1.00000	0.08525	0.08046	0.	1.00000	0.	1.00000	1.00000	0.	0.08593
FIT DEAD	1.7	1.8	1.7	0.5	1.9	1.6	1.1	1.8	0.6	1.7
FIT EE	14.5	17.2	35.4	17.7	25.3	6.9	5.7	19.0	8.5	9.4
FIT RATE	0.10492	0.09392	0.04453	0.02675	0.06830	0.18459	0.16764	0.08647	0.07088	0.15373
RISK B,AGE 50-69										
OBS RATE	0.07825	0.03775	0.06502	0.04149	0.03558	0.52611	0.03726	0.09608	1.00000	0.27011
FIT DEAD	6.5	3.8	9.2	2.8	5.1	6.0	2.5	10.0	3.8	4.7
FIT EE	62.1	44.2	116.4	54.9	87.8	29.6	14.7	62.5	26.2	32.8
FIT RATE	0.09437	0.07949	0.07292	0.04919	0.05476	0.16753	0.14369	0.13774	0.12554	0.12553
RISK B,AGE 70+										
OBS RATE	0.23069	0.21848	0.19457	1.00000	0.05504	0.12919	1.00000	0.14669	1.00000	0.15827
FIT DEAD	7.1	6.0	11.4	3.8	7.5	6.5	3.9	12.5	5.0	6.9
FIT EE	52.7	32.1	95.8	46.3	103.5	25.2	10.6	51.4	22.1	38.6
FIT RATE	0.11831	0.15854	0.10664	0.07541	0.06727	0.20581	0.26800	0.19512	0.18456	0.15162

TABLE 22.--FITTED DEATH RATES FOR CHOLECYSTECTOMIES RISK A, AGE 0-49, AGE 50-69

	H	N-B	C	E	O
	Operation code 40: Cholecystectomy alone				
Age 0-49:	Female 0.0005 (8)*	0.0007 (7)	0.0004 (10)	0.0004 (4)	0.0018 (3)
	Male 0.0010 (4)	0.0014 (2)	0.0007 (5)	0.0010 (2)	0.0043 (1)
Age 50-69:	Female 0.0028 (10)	0.0034 (5)	0.0035 (9)	0.0040 (4)	0.0080 (3)
	Male 0.0054 (5)	0.0067 (2)	0.0071 (5)	0.0112 (2)	0.0196 (1)
	Operation code 41: Cholecystectomy and/or bile duct				
Age 0-49:	Female 0.0021 (3)	0.0031 (3)	0.0018 (3)	0.0014 (1)	0.0034 (1)
	Male 0.0041 (2)	0.0061 (1)	0.0036 (1)	0.0039 (1)	0.0085 (1)
Age 50-69	Female 0.0101 (4)	0.0139 (3)	0.0159 (3)	0.0142 (1)	0.0144 (1)
	Male 0.0193 (2)	0.0267 (1)	0.0317 (1)	0.0384 (1)	0.0350 (1)
	Operation code 42: Cholecystectomy and/or bile duct, and other major procedures				
Age 0-49:	Female 0.0064 (2)	0.0058 (3)	0.0034 (3)	0.0025 (2)	0.0073 (2)
	Male 0.0122 (1)	0.0111 (1)	0.0069 (2)	0.0070 (1)	0.0179 (1)
Age 50-69:	Female 0.0211 (4)	0.0180 (3)	0.0213 (4)	0.0177 (3)	0.0215 (2)
	Male 0.0400 (2)	0.0343 (1)	0.0424 (2)	0.0475 (1)	0.0516 (1)

*Numbers in parentheses are estimated exposed in hundreds.

TABLE 23.--SUMS OF RANKS OF CRUDE DEATH RATES FOR CHOLECYSTECTOMIES BY AGENT FOR CATEGORIES HAVING AT LEAST 300 ESTIMATED EXPOSED

Operation code	H	N-B	C	E	Total
40	18.5	21.5	28	22	90 (9 rows)
41	14	14	13	19	60 (6 rows)
42	21	19.5	23	26.5	90 (9 rows)
Totals	53.5	55	64	67.5	240

for choosing among the four agents, but if one had to choose, halothane looks best except for operation code 42, where, of course, the cases are few and the estimates unreliable. The agent Other had a systematically high set of death rates.

We want to get a general notion of the ranking of halothane, nitrous oxide-barbiturate, cyclopropane, and ether. For each operation code-sex-risk-age category of Table 21 that contains at least 300 estimated exposed, spread among all agents, we ranked the crude death rates from least to greatest. These ranks were then summed for each operation to give the totals shown in Table 23. On this measure, halothane and nitrous oxide-barbiturate perform about equally well and slightly better than cyclopropane and ether.

HIGH-DEATH-RATE OPERATIONS

We wish primarily to supply some general information gained in the Study, rather than to compare anesthetic agents, when we give smoothed death rates for the four high-death-rate operations:

code 48: large bowel,
code 44: exploratory laparotomy, etc.,
code 12: craniotomy, and
code 33: heart and great vessel with pump.

In deciding whether to recommend an operative procedure at a given time, a physician or surgeon might wish to consult a death-rate table in which he can allow for the patient's anesthetic risk (physical status), sex, and age. In doing this, he will probably also have to consider at least whether the hospital or surgeon has a higher or a lower death rate than the average of the hospitals in this Study and whether the technology associated with these operation codes has improved much since the years on which these data are based (1958-1962). The latter point also suggests that these data offer something in the way of a baseline for these high-death-rate operations.

Table 24 gives death rates for the four high-death-rate operation codes. About 60 percent of the 60,000 cases in Table 24 are contained in the eight lines reproduced in Table 25. Recall that, because we use deaths/(deaths + EE) as the index of death rate, the rate r tends in the high-death-rate operations to be somewhat lower than the correct rate. To convert to the usual D/EE, one uses r/(1-r); for example, if our tabled rate is 0.2, then the usual rate is 0.2/(1-0.2) = 0.25.

Table 26 gives the fitted death rates for the high-death-rate operation codes with the agent included in the fitting. The data were somewhat

TABLE 24.--OBSERVED RATES AND RATES FITTED TO 4 VARIABLES: SEX, RISK, AGE, AND OPERATION CODE, HIGH-DEATH-RATE OPERATIONS, MODEL A

	OP 48	OP 44	OP 12	OP 33	OP 48	OP 44	OP 12	OP 33
			FEMALE				MALE	
RISK U,AGE 0- 9								
OBS RATE	0.07622	0.08595	0.08157	0.19457	0.01748	0.04290	0.09900	0.08192
FIT DEAD	3.9	8.8	13.8	58.3	3.9	9.9	18.2	74.2
FIT EE	102.0	149.6	250.3	466.7	107.0	130.4	244.1	503.8
FIT RATE	0.03682	0.05556	0.05241	0.11099	0.03522	0.07056	0.06925	0.12840
RISK U,AGE 10-49								
OBS RATE	0.03995	0.02130	0.09973	0.16226	0.07320	0.09579	0.13762	0.21580
FIT DEAD	9.9	25.2	48.9	92.2	8.9	25.5	57.7	105.6
FIT EE	267.6	538.3	415.8	482.2	226.7	379.1	327.5	420.5
FIT RATE	0.03581	0.04476	0.10528	0.16053	0.03796	0.06304	0.14974	0.20068
RISK U,AGE 50-69								
OBS RATE	0.03087	0.07969	0.07038	0.23687	0.05290	0.10131	0.18755	0.17138
FIT DEAD	26.0	44.3	40.0	22.4	28.8	55.1	57.9	31.5
FIT EE	695.6	755.9	380.0	101.9	541.9	489.5	275.3	81.7
FIT RATE	0.03607	0.05542	0.09514	0.18030	0.05044	0.10116	0.17371	0.27841
RISK U,AGE 70+								
OBS RATE	0.04897	0.09583	1.00000	0.	0.16489	0.17009	0.16839	0.
FIT DEAD	26.7	28.7	5.3	0.4	27.7	33.3	7.2	0.6
FIT EE	310.8	247.8	36.9	0.	256.6	170.0	28.3	0.
FIT RATE	0.07914	0.10370	0.12637	1.00000	0.09729	0.16395	0.20354	1.00000
RISK A,AGE 0- 9								
OBS RATE	0.01136	0.03914	0.02644	0.08608	0.02010	0.03272	0.05721	0.12428
FIT DEAD	7.9	12.5	30.1	45.5	7.8	13.8	38.6	56.7
FIT EE	280.9	297.2	780.8	353.9	356.5	313.4	921.0	462.2
FIT RATE	0.02747	0.04052	0.03711	0.11403	0.02133	0.04218	0.04021	0.10931
RISK A,AGE 10-49								
OBS RATE	0.01396	0.02126	0.04584	0.10196	0.00996	0.01666	0.04422	0.09469
FIT DEAD	23.4	41.7	123.2	83.5	20.6	41.2	141.9	93.5
FIT EE	1665.1	2416.9	2931.0	826.5	1706.5	2058.7	2792.6	871.8
FIT RATE	0.01387	0.01695	0.04033	0.09178	0.01193	0.01961	0.04837	0.09683
RISK A,AGE 50-69								
OBS RATE	0.02364	0.02969	0.06831	0.28415	0.02729	0.07033	0.08660	0.19106
FIT DEAD	66.3	79.2	108.7	21.9	71.7	96.1	153.9	30.2
FIT EE	2695.9	2113.9	1668.5	108.8	2540.7	1655.8	1462.0	105.5
FIT RATE	0.02400	0.03610	0.06116	0.16783	0.02744	0.05488	0.09525	0.22231
RISK A,AGE 70+								
OBS RATE	0.04489	0.04867	0.02665	1.00000	0.04827	0.09537	0.12175	0.
FIT DEAD	53.7	40.4	11.5	0.3	54.4	46.0	15.2	0.4
FIT EE	1221.2	702.3	164.3	0.	1219.8	583.1	152.6	0.
FIT RATE	0.04215	0.05442	0.06528	1.00000	0.04269	0.07307	0.09066	1.00000

Table 24 (Cont'd)

	OP 48	OP 44	OP 12	OP 33	OP 48	OP 44	OP 12	OP 33
	FEMALE				MALE			
RISK B,AGE 0- 9								
OBS RATE	0.21198	0.13568	0.07142	0.18762	0.10975	0.35889	0.13598	0.23285
FIT DEAD	9.6	23.7	30.1	116.8	9.8	27.1	40.2	151.6
FIT EE	51.6	97.7	215.8	465.3	68.7	108.1	267.1	637.7
FIT RATE	0.15729	0.19485	0.12247	0.20070	0.12512	0.20039	0.13092	0.19208
RISK B,AGE 10-49								
OBS RATE	0.10091	0.10413	0.11834	0.14382	0.06909	0.10158	0.17137	0.19208
FIT DEAD	29.7	82.0	128.7	223.7	27.2	84.4	154.5	260.8
FIT EE	311.5	809.7	825.0	1107.0	334.9	723.7	824.8	1225.3
FIT RATE	0.08698	0.09196	0.13494	0.16809	0.07512	0.10449	0.15778	0.17550
RISK B,AGE 50-69								
OBS RATE	0.11360	0.14867	0.18247	0.28189	0.12221	0.19529	0.22965	0.27357
FIT DEAD	91.4	169.6	123.6	63.9	103.0	214.6	182.4	91.6
FIT EE	707.1	992.9	658.6	204.2	699.3	816.2	605.5	207.9
FIT RATE	0.11447	0.14587	0.15804	0.23839	0.12835	0.20816	0.23147	0.30583
RISK B,AGE 70+								
OBS RATE	0.17971	0.20384	0.19412	1.00000	0.13601	0.17138	0.20816	1.00000
FIT DEAD	127.3	148.7	22.4	1.7	134.3	176.2	31.0	2.3
FIT EE	702.4	723.5	142.2	0.	736.2	630.2	138.6	0.
FIT RATE	0.15342	0.17053	0.13618	1.00000	0.15425	0.21852	0.18268	1.00000
RISK C,AGE 0- 9								
OBS RATE	1.00000	1.00000	1.00000	1.00000	1.00000	0.30435	1.00000	1.00000
FIT DEAD	1.8	6.5	9.8	2.7	2.2	8.7	15.2	4.1
FIT EE	0.2	2.0	3.6	1.6	0.7	4.7	9.8	4.8
FIT RATE	0.88563	0.76893	0.73016	0.62614	0.75980	0.64752	0.60891	0.45810
RISK C,AGE 10-49								
OBS RATE	1.00000	0.45609	0.56251	0.34851	1.00000	0.49629	0.34436	0.15575
FIT DEAD	6.9	27.3	50.5	6.2	7.3	32.7	70.6	8.5
FIT EE	3.9	44.2	37.7	10.4	9.2	86.3	82.4	25.2
FIT RATE	0.63643	0.38147	0.57253	0.37378	0.44308	0.27474	0.46164	0.25106
RISK C,AGE 50-69								
OBS RATE	0.35865	0.56330	0.57412	1.00000	0.74756	0.24692	0.62057	0.47134
FIT DEAD	15.5	41.3	35.5	1.3	20.3	60.8	61.0	2.2
FIT EE	10.1	61.7	34.2	2.2	21.9	110.7	68.8	4.9
FIT RATE	0.60461	0.40102	0.50923	0.37315	0.48147	0.35460	0.47021	0.30875
RISK C,AGE 70+								
OBS RATE	0.41367	0.31044	0.49669	0.	0.55258	0.33887	1.00000	1.00000
FIT DEAD	19.7	33.1	5.9	0.0	24.2	45.6	9.5	0.1
FIT EE	12.2	54.4	8.9	0.	27.9	103.5	19.0	0.
FIT RATE	0.61781	0.37803	0.39655	1.00000	0.46446	0.30589	0.33184	1.00000

TABLE 25.--FITTED DEATH RATES IN LARGE CELLS FOR HIGH-DEATH-RATE OPERATIONS, MODEL A

Risk level: A = risks 1 + 2 + 5
B = risks 3 + 4 + 6

Risk	Sex	Age	Operation code			
			48	44	12	33
A	f	0-9	0.027 (3)*	0.041 (3)	0.037 (8)	0.114 (4)
A	m	0-9	0.021 (4)	0.042 (3)	0.040 (9)	0.109 (5)
A	f	10-49	0.014 (17)	0.017 (24)	0.040 (29)	0.092 (8)
A	m	10-49	0.012 (17)	0.020 (21)	0.048 (28)	0.097 (9)
A	f	50-69	0.024 (27)	0.036 (21)	0.061 (17)	0.168 (1)
A	m	50-69	0.027 (25)	0.055 (17)	0.095 (15)	0.222 (1)
B	f	10-49	0.087 (3)	0.092 (8)	0.135 (8)	0.168 (11)
B	m	10-49	0.075 (3)	0.104 (7)	0.158 (8)	0.175 (12)

*Numbers in parentheses are estimated exposed in hundreds.

patchy, so we had to adopt an additional smoothing device. We added 4 to the number of deaths in every cell and 40 to the estimated exposed in every cell before fitting the model. These numbers were removed after fitting and so occasionally produced negative estimated cell values. Where negative values occur in the table, the fitted rate appears as 9.99999, a signal that no useful estimate appeared.

The largest cells from Table 26 have been abstracted to give Table 27. The most striking feature of Table 27 is the very great increase in death rate for older persons and persons rated as being poorer risks.

These four operations were separated from the main body of data because they contained so many deaths, but the operations themselves are not closely related to each other. It is therefore desirable to consider agent differences separately for each operation.

For operation 48 (large bowel), for all but the youngest age group, halothane and nitrous oxide-barbiturate, on the whole, had the lowest rates, and Other had the highest rates.

For operation 44 (exploratory laparotomy), ether seems to have had the lowest rates, followed by halothane and nitrous oxide-barbiturate. Recall that our ether rates are poorly determined. Cyclopropane appears to have had the highest rates.

Cyclopropane was rarely used for operation 12 (craniotomy). For the four large cells with ages 10 and over, ether had the lowest rates. The other three agent categories did not show consistent differences.

For operation 33 (heart and great vessel with pump), in the three cells listed nitrous oxide-barbiturate had the highest rates; halothane, cyclopropane, and Other had similar rates; and ether was seldom used.

Table 28 gives the rankings of anesthetic agents (excluding Other) by observed death rates in the high-death-rate operations for rows of Table 26 having at least 1000 estimated exposed. Rank 1 was assigned to the agent with lowest death rate, rank 2 to the next lowest, and so on. The ranks were then summed. We note that for operation 48 (large bowel), halothane has the lowest score of the four agents. For operation 44 (exploratory laparotomy), halothane is tied with ether for the lowest. Ether had the lowest score for operation 12 (craniotomy); cyclopropane had the lowest score for operation 33 (heart with pump), although there were few cases.

TABLE 26.--OBSERVED RATES AND RATES FITTED TO 4 VARIABLES: AGENT, RISK, AGE, AND OPERATION CODE, HIGH-DEATH-RATE OPERATIONS, MODEL B

OPERATION CODE 48

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.07692	0.	0.05556	1.00000	0.01000
FIT DEAD	2.3	-0.3	0.9	2.1	3.0
FIT EE	60.3	11.4	30.0	31.2	140.0
FIT RATE	0.03729	9.99999	0.03060	0.06237	0.02080
RISK U,AGE 10-49					
OBS RATE	0.08989	0.01875	0.07059	0.02857	0.11111
FIT DEAD	5.6	4.1	7.7	1.1	1.4
FIT EE	93.9	84.8	129.0	26.3	33.0
FIT RATE	0.05666	0.04639	0.05663	0.03976	0.04075
RISK U,AGE 50-69					
OBS RATE	0.01927	0.02579	0.08962	0.05369	0.05747
FIT DEAD	13.3	9.0	19.0	4.9	4.9
FIT EE	446.3	362.7	210.4	121.3	124.4
FIT RATE	0.02884	0.02415	0.08267	0.03867	0.03818
RISK U,AGE 70+					
OBS RATE	0.15054	0.18367	0.05538	0.04505	0.13253
FIT DEAD	12.8	8.2	18.3	7.0	10.7
FIT EE	92.6	78.1	260.6	102.1	70.6
FIT RATE	0.12127	0.09534	0.06579	0.06375	0.13146
RISK A,AGE 0- 9					
OBS RATE	0.02283	0.	0.01235	0.01105	0.01429
FIT DEAD	4.6	0.6	1.4	1.7	0.6
FIT EE	179.3	21.9	85.2	153.4	115.2
FIT RATE	0.02517	0.02594	0.01639	0.01119	0.00545
RISK A,AGE 10-49					
OBS RATE	0.00988	0.01316	0.01716	0.00800	0.00833
FIT DEAD	10.1	6.6	16.1	6.0	4.3
FIT EE	757.5	556.6	1070.2	641.6	529.2
FIT RATE	0.01319	0.01164	0.01480	0.00919	0.00805
RISK A,AGE 50-69					
OBS RATE	0.02245	0.01854	0.03401	0.01933	0.03333
FIT DEAD	29.6	19.3	40.9	19.1	25.1
FIT EE	1338.3	914.8	1284.3	924.2	665.4
FIT RATE	0.02161	0.02068	0.03083	0.02026	0.03642
RISK A,AGE 70+					
OBS RATE	0.05411	0.05236	0.02621	0.05596	0.07645
FIT DEAD	24.7	18.5	31.7	21.2	23.9
FIT EE	476.0	337.7	935.2	380.9	323.2
FIT RATE	0.04930	0.05206	0.03274	0.05272	0.06892

OPERATION CODE 48

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.18182	0.	0.17241	0.08750	0.42857
FIT DEAD	7.5	-0.1	7.6	6.6	4.4
FIT EE	34.3	-17.0	53.5	50.5	19.7
FIT RATE	0.17958	9.99999	0.12475	0.11511	0.18328
RISK B,AGE 10-49					
OBS RATE	0.12048	0.07438	0.07965	0.05747	0.21875
FIT DEAD	11.2	7.9	25.9	5.4	7.6
FIT EE	119.8	78.7	266.9	70.6	68.0
FIT RATE	0.08522	0.09149	0.08850	0.07076	0.10080
RISK B,AGE 50-69					
OBS RATE	0.07906	0.14286	0.11342	0.16867	0.15646
FIT DEAD	35.5	26.8	76.6	15.7	43.5
FIT EE	406.9	244.9	520.4	89.9	221.0
FIT RATE	0.08020	0.09849	0.12838	0.14847	0.16433
RISK B,AGE 70+					
OBS RATE	0.11528	0.08541	0.23469	0.16964	0.14560
FIT DEAD	43.9	28.4	84.8	36.4	56.5
FIT EE	309.0	242.4	350.2	199.1	283.4
FIT RATE	0.12427	0.10503	0.19497	0.15453	0.16627
RISK C,AGE 0- 9					
OBS RATE	0.	0.	1.00000	1.00000	0.
FIT DEAD	0.5	-0.1	0.0	2.6	1.0
FIT EE	0.1	-3.3	-13.8	16.9	0.1
FIT RATE	0.81128	9.99999	9.99999	0.13429	0.94524
RISK C,AGE 10-49					
OBS RATE	1.00000	1.00000	1.00000	1.00000	1.00000
FIT DEAD	0.1	2.4	7.3	0.6	2.7
FIT EE	-15.2	-1.1	12.8	-2.4	5.9
FIT RATE	9.99999	9.99999	0.36195	9.99999	0.31319
RISK C,AGE 50-69					
OBS RATE	1.00000	1.00000	0.73077	1.00000	0.23810
FIT DEAD	2.7	6.0	17.5	3.3	10.5
FIT EE	11.6	3.6	17.9	-12.4	18.3
FIT RATE	0.18940	0.62235	0.49475	9.99999	0.36427
RISK C,AGE 70+					
OBS RATE	1.00000	0.50000	0.25490	1.00000	1.00000
FIT DEAD	3.7	5.8	13.2	3.5	14.9
FIT EE	3.5	8.8	28.1	-2.1	7.8
FIT RATE	0.51595	0.39725	0.31985	9.99999	0.65634

Table 26 (Cont'd)

OPERATION CODE 44

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.03947	0.	0.05941	0.12000	0.05392
FIT DEAD	5.3	0.9	4.0	4.1	11.8
FIT EE	59.8	10.1	90.6	23.9	220.7
FIT RATE	0.08094	0.07784	0.04267	0.14573	0.05066
RISK U,AGE 10-49					
OBS RATE	0.05903	0.09783	0.02476	0.11111	0.03077
FIT DEAD	14.9	9.1	14.3	1.7	5.0
FIT EE	277.1	106.7	463.0	58.6	102.5
FIT RATE	0.05101	0.07862	0.02990	0.02818	0.04678
RISK U,AGE 50-69					
OBS RATE	0.10465	0.09091	0.12052	0.03867	0.06215
FIT DEAD	26.3	18.7	38.4	9.4	10.3
FIT EE	266.7	182.5	293.7	143.6	164.3
FIT RATE	0.08970	0.09285	0.11553	0.06115	0.05903
RISK U,AGE 70+					
OBS RATE	0.10345	0.31250	0.13014	0.03846	0.15854
FIT DEAD	12.6	11.4	18.3	2.9	11.9
FIT EE	75.4	15.7	156.6	82.9	66.4
FIT RATE	0.14280	0.41948	0.10475	0.03353	0.15172
RISK A,AGE 0- 9					
OBS RATE	0.03497	0.02174	0.03774	0.04040	0.03425
FIT DEAD	3.9	0.4	4.6	4.2	5.8
FIT EE	164.9	37.2	93.6	101.9	123.4
FIT RATE	0.02338	0.01114	0.04725	0.03953	0.04489
RISK A,AGE 10-49					
OBS RATE	0.01296	0.01488	0.02491	0.02422	0.01770
FIT DEAD	17.8	11.5	34.4	11.0	12.2
FIT EE	1308.3	642.7	1396.2	590.6	574.2
FIT RATE	0.01346	0.01762	0.02402	0.01832	0.02088
RISK A,AGE 50-69					
OBS RATE	0.03660	0.03304	0.05860	0.03229	0.06065
FIT DEAD	28.9	22.3	68.0	29.2	34.7
FIT EE	792.4	649.4	989.3	876.0	609.9
FIT RATE	0.03517	0.03323	0.06428	0.03221	0.05381
RISK A,AGE 70+					
OBS RATE	0.02500	0.09444	0.10000	0.02844	0.08962
FIT DEAD	11.3	13.7	26.0	10.6	20.3
FIT EE	334.4	162.7	283.9	224.5	185.6
FIT RATE	0.03276	0.07784	0.08400	0.04522	0.09850

OPERATION CODE 44

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.23333	0.	0.19118	0.25532	0.26000
FIT DEAD	6.8	-0.1	13.8	12.3	12.3
FIT EE	12.1	-7.9	60.2	43.6	42.0
FIT RATE	0.35940	9.99999	0.18625	0.21947	0.22585
RISK B,AGE 10-49					
OBS RATE	0.09202	0.15033	0.10831	0.06504	0.11157
FIT DEAD	30.0	22.1	73.9	17.6	25.5
FIT EE	287.9	205.7	604.6	168.1	205.7
FIT RATE	0.09421	0.09690	0.10888	0.09489	0.11023
RISK B,AGE 50-69					
OBS RATE	0.14939	0.11084	0.22292	0.24051	0.13873
FIT DEAD	51.0	46.6	169.0	38.3	76.1
FIT EE	266.3	307.8	621.1	194.6	434.2
FIT RATE	0.16067	0.13157	0.21387	0.16450	0.14912
RISK B,AGE 70+					
OBS RATE	0.14332	0.13880	0.36677	0.12045	0.17043
FIT DEAD	42.3	43.4	123.4	40.8	81.2
FIT EE	294.7	258.4	189.1	292.7	421.1
FIT RATE	0.12545	0.14377	0.39484	0.12233	0.16161
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	1.00000	1.00000	0.25000
FIT DEAD	3.0	-0.2	5.5	4.5	8.2
FIT EE	-2.8	5.6	7.6	4.7	11.9
FIT RATE	9.99999	9.99999	0.42107	0.48997	0.40653
RISK C,AGE 10-49					
OBS RATE	0.42857	0.31579	0.42667	1.00000	1.00000
FIT DEAD	7.3	6.3	30.5	2.7	12.2
FIT EE	-3.4	-1.1	62.2	-7.3	13.6
FIT RATE	9.99999	9.99999	0.32910	9.99999	0.47378
RISK C,AGE 50-69					
OBS RATE	0.35000	0.28947	0.33784	1.00000	0.22353
FIT DEAD	7.9	8.4	51.7	6.2	19.9
FIT EE	13.6	14.3	92.8	8.7	74.6
FIT RATE	0.36615	0.36909	0.35771	0.41494	0.21077
RISK C,AGE 70+					
OBS RATE	0.31034	1.00000	0.32075	0.16129	0.33750
FIT DEAD	7.9	9.5	33.3	2.7	28.7
FIT EE	33.6	21.2	50.4	20.0	45.9
FIT RATE	0.18953	0.30996	0.39762	0.11892	0.38452

Table 26 (Cont'd)

OPERATION CODE 12

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.11111	1.00000	0.28571	0.15625	0.04348
FIT DEAD	14.5	1.3	2.9	5.9	10.4
FIT EE	125.6	20.1	13.0	20.2	167.1
FIT RATE	0.10330	0.06181	0.18388	0.22477	0.05869
RISK U,AGE 10-49					
OBS RATE	0.10286	0.10619	0.16667	0.05208	0.37500
FIT DEAD	60.0	21.6	0.2	4.5	18.7
FIT EE	510.0	176.9	-6.4	66.3	57.2
FIT RATE	0.10533	0.10872	9.99999	0.06405	0.24604
RISK U,AGE 50-69					
OBS RATE	0.14835	0.07299	0.	0.08537	0.09160
FIT DEAD	55.4	20.2	-0.3	7.5	10.2
FIT EE	300.8	268.2	-9.3	119.6	78.7
FIT RATE	0.15559	0.06990	9.99999	0.05905	0.11515
RISK U,AGE 70+					
OBS RATE	0.35294	1.00000	0.	0.03571	1.00000
FIT DEAD	10.1	3.9	0.2	0.1	1.7
FIT EE	26.5	-9.2	12.8	13.9	5.0
FIT RATE	0.27487	9.99999	0.01837	0.00668	0.24997
RISK A,AGE 0- 9					
OBS RATE	0.03668	0.04975	0.05102	0.04712	0.05525
FIT DEAD	42.8	11.3	5.4	10.1	6.4
FIT EE	1131.5	178.1	58.9	197.9	173.6
FIT RATE	0.03642	0.05982	0.08354	0.04858	0.03568
RISK A,AGE 10-49					
OBS RATE	0.03947	0.05636	0.18750	0.03025	0.09355
FIT DEAD	148.8	63.1	3.7	18.2	29.2
FIT EE	3685.7	1059.9	41.0	518.5	278.9
FIT RATE	0.03882	0.05618	0.08311	0.03382	0.09477
RISK A,AGE 50-69					
OBS RATE	0.09091	0.06641	0.13333	0.04602	0.11157
FIT DEAD	141.9	63.9	2.0	26.8	30.3
FIT EE	1355.0	944.6	35.8	579.7	232.0
FIT RATE	0.09481	0.06338	0.05354	0.04420	0.11560
RISK A,AGE 70+					
OBS RATE	0.04453	0.09615	0.	0.07143	0.
FIT DEAD	11.5	7.7	-1.1	0.9	0.1
FIT EE	251.8	63.4	22.3	40.9	21.6
FIT RATE	0.04351	0.10778	9.99999	0.02237	0.00271

OPERATION CODE 12

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.09551	0.07895	1.00000	0.10145	0.09184
FIT DEAD	36.7	4.5	3.4	12.0	10.4
FIT EE	314.0	66.5	27.9	122.5	74.1
FIT RATE	0.10476	0.06350	0.10837	0.08896	0.12301
RISK B,AGE 10-49					
OBS RATE	0.12552	0.14133	1.00000	0.12397	0.31944
FIT DEAD	149.6	67.4	2.1	14.4	46.6
FIT EE	998.6	409.1	-7.9	166.3	91.0
FIT RATE	0.13029	0.14138	9.99999	0.07950	0.33877
RISK B,AGE 50-69					
OBS RATE	0.28182	0.13619	1.00000	0.09091	0.31319
FIT DEAD	153.0	78.4	1.6	18.6	55.4
FIT EE	476.1	454.4	-2.3	115.9	138.8
FIT RATE	0.24321	0.14717	9.99999	0.13796	0.28539
RISK B,AGE 70+					
OBS RATE	0.15169	0.28571	0.	1.00000	0.25714
FIT DEAD	27.6	16.7	1.0	5.1	8.5
FIT EE	131.3	59.0	-17.7	25.3	34.1
FIT RATE	0.17390	0.22072	9.99999	0.16855	0.20040
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	1.00000	1.00000	1.00000
FIT DEAD	9.0	-0.2	0.3	3.1	5.8
FIT EE	13.8	-3.6	-1.8	-7.6	-0.8
FIT RATE	0.39442	9.99999	9.99999	9.99999	9.99999
RISK C,AGE 10-49					
OBS RATE	0.37500	0.29870	1.00000	1.00000	0.46535
FIT DEAD	48.5	23.0	2.1	6.0	48.5
FIT EE	88.7	49.1	-8.6	22.9	40.9
FIT RATE	0.35348	0.31875	9.99999	0.20626	0.54259
RISK C,AGE 50-69					
OBS RATE	0.48684	1.00000	0.	1.00000	0.57377
FIT DEAD	36.6	18.5	0.7	7.1	35.0
FIT EE	22.0	19.7	-11.1	-1.2	35.6
FIT RATE	0.62469	0.48384	9.99999	9.99999	0.49600
RISK C,AGE 70+					
OBS RATE	0.38462	1.00000	0.	0.	1.00000
FIT DEAD	5.8	2.7	-0.1	-1.2	6.7
FIT EE	7.4	-11.2	21.6	-14.1	4.3
FIT RATE	0.44101	9.99999	9.99999	9.99999	0.61001

Table 26 (Cont'd)

OPERATION CODE 33

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK U,AGE 0- 9					
OBS RATE	0.10593	0.05063	0.20213	0.	0.11526
FIT DEAD	27.9	3.2	22.2	-0.0	68.8
FIT EE	222.4	33.4	92.4	-4.3	585.1
FIT RATE	0.11155	0.08613	0.19345	9.99999	0.10519
RISK U,AGE 10-49					
OBS RATE	0.15563	0.31325	0.30769	1.00000	0.31250
FIT DEAD	132.4	27.2	9.8	2.7	31.9
FIT EE	669.0	130.6	37.4	-10.2	50.3
FIT RATE	0.16525	0.17220	0.20843	9.99999	0.38802
RISK U,AGE 50-69					
OBS RATE	0.21176	0.04000	0.07692	0.	1.00000
FIT DEAD	50.1	3.2	0.9	0.3	4.5
FIT EE	237.1	14.5	-7.8	5.4	-0.3
FIT RATE	0.17434	0.18030	9.99999	0.04513	9.99999
RISK U,AGE 70+					
OBS RATE	0.	0.	0.	0.	0.
FIT DEAD	2.6	-2.5	0.0	-0.9	0.8
FIT EE	10.5	-22.6	4.0	9.1	-1.0
FIT RATE	0.19900	9.99999	0.01179	9.99999	9.99999
RISK A,AGE 0- 9					
OBS RATE	0.07063	0.18605	0.21831	0.	0.05672
FIT DEAD	19.6	30.6	29.6	-1.0	30.1
FIT EE	229.2	151.8	148.3	2.8	417.9
FIT RATE	0.07889	0.16797	0.16646	9.99999	0.06729
RISK A,AGE 10-49					
OBS RATE	0.08016	0.11733	0.05769	0.	0.12987
FIT DEAD	58.2	85.8	11.9	1.9	18.3
FIT EE	697.5	618.8	110.6	10.3	182.8
FIT RATE	0.07698	0.12174	0.09705	0.15480	0.09091
RISK A,AGE 50-69					
OBS RATE	0.20192	0.34000	0.13333	0.	0.16216
FIT DEAD	21.7	18.5	1.1	-0.1	4.8
FIT EE	86.4	56.2	6.5	1.1	9.7
FIT RATE	0.20048	0.24746	0.14346	9.99999	0.33248
RISK A,AGE 70+					
OBS RATE	0.	0.	1.00000	0.	0.
FIT DEAD	-0.4	2.1	0.4	-0.8	-0.3
FIT EE	-3.1	8.2	5.5	-14.3	3.6
FIT RATE	9.99999	0.20326	0.06588	9.99999	9.99999

OPERATION CODE 33

	AGENT 1	AGENT 2	AGENT 3	AGENT 4	AGENT 5
RISK B,AGE 0- 9					
OBS RATE	0.21713	0.27064	0.18157	1.00000	0.18868
FIT DEAD	69.0	60.8	64.1	6.2	71.0
FIT EE	276.5	187.4	239.3	15.4	299.3
FIT RATE	0.19964	0.24482	0.21115	0.28720	0.19170
RISK B,AGE 10-49					
OBS RATE	0.12803	0.19887	0.16667	1.00000	0.17593
FIT DEAD	169.3	247.7	21.1	7.6	38.3
FIT EE	1165.7	944.5	154.4	13.1	151.3
FIT RATE	0.12683	0.20777	0.12005	0.36821	0.20186
RISK B,AGE 50-69					
OBS RATE	0.19940	0.33663	1.00000	1.00000	1.00000
FIT DEAD	68.5	64.1	5.0	2.5	14.0
FIT EE	224.8	130.9	32.8	-11.4	26.0
FIT RATE	0.23346	0.32878	0.13134	9.99999	0.35043
RISK B,AGE 70+					
OBS RATE	1.00000	1.00000	0.	0.	1.00000
FIT DEAD	1.2	3.4	-0.1	-0.3	-0.3
FIT EE	9.1	25.2	-19.5	-17.1	2.3
FIT RATE	0.12025	0.11897	9.99999	9.99999	9.99999
RISK C,AGE 0- 9					
OBS RATE	1.00000	0.	1.00000	0.	1.00000
FIT DEAD	0.5	0.5	3.2	-1.2	5.1
FIT EE	-11.2	1.4	8.0	-13.9	15.8
FIT RATE	9.99999	0.25032	0.28443	9.99999	0.24376
RISK C,AGE 10-49					
OBS RATE	1.00000	0.31579	0.	0.	0.25000
FIT DEAD	4.1	6.3	-0.8	-1.2	1.6
FIT EE	22.8	33.0	0.7	-13.2	-0.4
FIT RATE	0.15190	0.16066	9.99999	9.99999	9.99999
RISK C,AGE 50-69					
OBS RATE	0.25000	1.00000	0.	0.	1.00000
FIT DEAD	3.8	2.2	-1.0	0.4	0.6
FIT EE	10.8	-10.7	5.4	4.9	-4.4
FIT RATE	0.26219	9.99999	9.99999	0.06969	9.99999
RISK C,AGE 70+					
OBS RATE	1.00000	0.	0.	0.	0.
FIT DEAD	-1.4	-1.0	0.6	2.0	0.7
FIT EE	-16.5	-10.7	10.0	22.2	-5.0
FIT RATE	9.99999	9.99999	0.05900	0.08252	9.99999

TABLE 27.--FITTED DEATH RATES PER 100 IN LARGE CELLS FOR HIGH-DEATH-RATE OPERATIONS, MODEL B

Risk level: U = unknown
A = risks 1 + 2 + 5
B = risks 3 + 4 + 6

Risk	Age	H	N-B	C	E	O
	Operation code 48: Large bowel					
U	50-69	2.9 (4)*	2.4 (4)	8.3 (2)	3.9 (1)	3.8 (1)
A	10-49	1.3 (8)	1.2 (6)	1.5 (11)	0.9 (6)	0.8 (5)
A	50-69	2.2 (13)	2.1 (9)	3.1 (13)	2.0 (9)	3.6 (7)
A	70 +	4.9 (5)	5.2 (3)	3.3 (9)	5.3 (4)	6.9 (3)
B	50-69	8.0 (4)	9.8 (2)	12.8 (5)	14.8 (1)	16.4 (2)
B	70 +	12.4 (3)	10.5 (2)	19.5 (4)	15.5 (2)	16.6 (3)
	Operation code 44: Exploratory laparotomy, etc.					
U	10-49	5.1 (3)	7.9 (1)	3.0 (5)	2.8 (1)	4.7 (1)
U	50-69	9.0 (3)	9.3 (2)	11.6 (3)	6.1 (1)	5.9 (2)
A	10-49	1.3 (13)	1.8 (6)	2.4 (14)	1.8 (6)	2.1 (6)
A	50-69	3.5 (8)	3.3 (6)	6.4 (10)	3.2 (9)	5.4 (6)
A	70 +	3.3 (3)	7.8 (2)	8.4 (3)	4.5 (2)	9.9 (2)
B	10-49	9.4 (3)	9.7 (2)	10.9 (6)	9.5 (2)	11.0 (2)
B	50-69	16.1 (3)	13.2 (3)	21.4 (6)	16.5 (2)	14.9 (4)
B	70 +	12.5 (3)	14.4 (3)	39.5 (2)	12.2 (3)	16.2 (4)
	Operation code 12: Craniotomy					
	Age	H	N-B	C	E	O
A	0-9	3.6 (11)	6.0 (2)	8.4 (1)	4.9 (2)	3.6 (2)
A	10-49	3.9 (37)	5.6 (11)	8.3 (0)**	3.4 (5)	9.5 (3)
A	50-69	9.5 (14)	6.3 (9)	5.4 (0)***	4.4 (6)	11.6 (2)
B	10-49	13.0 (10)	14.1 (4)		8.0 (2)	3.4 (1)
B	50-69	24.3 (5)	14.7 (5)		13.8 (1)	28.5 (1)
	Operation code 33: Heart and great vessel with pump					
	Age	H	N-B	C	E	O
A	10-49	7.7 (7)	12.2 (6)	9.7 (1)		9.1 (2)
B	0-9	20.0 (3)	24.5 (2)	21.1 (2)		19.2 (3)
B	10-49	12.7 (12)	20.8 (9)	12.0 (2)		20.2 (2)

*Numbers in parentheses are estimated exposed in hundreds.
**41 estimated exposed.
***35 estimated exposed.

TABLE 28.--RANKINGS OF ANESTHETICS BY OBSERVED DEATH RATES IN THE HIGH-DEATH-RATE OPERATIONS FOR ROWS OF TABLE 26 HAVING AT LEAST 1000 ESTIMATED EXPOSED

Physical status	Age	Anesthetic H	N-B	C	E	
	Operation 48: Large bowel					
Unknown	50-69	1	2	4	3	
1, 2, 5	10-49	2	3	4	1	
1, 2, 5	50-69	3	1	4	2	
1, 2, 5	70+	3	2	1	4	
3, 4, 6	50-69	1	3	2	4	
3, 4, 6	70+	1	2	3	4	
Totals		11	13	18	18	60
	Operation 44: Exploratory laparotomy					
Unknown	10-49	2	3	1	4	
Unknown	50-69	3	2	4	1	
1, 2, 5	10-49	1	2	4	3	
1, 2, 5	50-69	3	2	4	1	
1, 2, 5	70+	1	3	4	2	
3, 4, 6	10-49	2	4	3	1	
3, 4, 6	50-69	2	1	3	4	
3, 4, 6	70+	3	2	4	1	
Totals		17	19	27	17	80
	Operation 12: Craniotomy					
1, 2, 5	0-9	1	3	(*)	2	
1, 2, 5	10-49	2	3	(*)	1	
1, 2, 5	50-69	3	2	(*)	1	
3, 4, 6	10-49	2	3	(*)	1	
3, 4, 6	50-69	3	2	(*)	1	
Totals		11	13	(*)	6	30
	Operation 33: Heart and great vessel with pump					
3, 4, 6	10-49	2	3	1	(*)	
3, 4, 6	0-9	2	3	1	(*)	
3, 4, 6	10-49	1	3	2	(*)	
Totals		5	9	4**	(*)	18

*Too seldom used to be ranked.
**Based on small numbers of cases.

CONCLUSIONS

In a complicated system requiring many variables for its description, one cannot expect a simple conclusion. Insofar as we can summarize, halothane showed up satisfactorily, cyclopropane and Other sometimes did not, and nitrous oxide-barbiturate and ether often had the lowest death rates.

For the low-death-rate operations, although the differences in rates were small, the order of increasing death rates seemed to be ether, nitrous oxide-barbiturate, halothane, cyclopropane.

For the middle-death-rate operations, halothane, ether, and nitrous oxide-barbiturate were associated with similar death rates, but cyclopropane and Other with higher rates.

For the cholecystectomies, although the differences in death rates between agents were not large, halothane had the lowest death rates for both "cholecystectomy alone" and "cholecystectomy and/or bile duct," but matters were not so clear for "cholecystectomy and/or bile duct, and other major procedures," where cases were fewer and the control poorer because of the great variety of "other major procedures." The results were a bit of a surprise because halothane is sometimes thought to be an undesirable anesthetic for use in cholecystectomies.

Among the high-death-rate operations, for large bowel, halothane and nitrous oxide-barbiturate had the lowest rates; for exploratory laparotomy, ether, then halothane, and nitrous oxide-barbiturate had the lower rates, and cyclopropane rates were high; for craniotomy, cyclopropane was rarely used, ether seems to have had the lowest rates (although not much used), and the other three agents did not

show consistent differences; and for heart and great vessel with pump, ether was rarely used and cyclopropane only occasionally, nitrous oxide-barbiturate had the highest rates, and halothane rates were similar to those for cyclopropane and Other.

As a final warning: (1) Death rates associated with ether were poorly determined because some institutions rarely used it. (2) The rates reported here are related to the choice of common practices in the institutions, and therefore may be subject to various sorts of biases that would be controlled only in a prospective randomized study. (3) The death rates are thought of as caused not by the anesthetics, but by the whole procedure, including the patient's disease; however, differences in death rates are an indication of deaths caused by anesthetic differences (plus some uncontrolled variables). (4) Observed differential death rates are not necessarily an automatic basis for changing medical practices, especially inasmuch as the training and skills of the practitioner must be considered, as well as the properties of the individual patient.

REFERENCE

1. Birch, M. W. Maximum likelihood in three-way contingency tables. J. Roy. Statist. Soc., Ser. B, 25:220-233, 1963.

APPENDIX TO CHAPTER IV-3

CALCULATING SMOOTHED CONTINGENCY TABLES

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This appendix describes briefly the theory behind the use of a linear model in the logarithmic scale for smoothing contingency tables. Several papers in the current literature deal with this approach, one of the most recent being that of Birch. His notation of "u-terms" has been adopted here. This appendix also describes the method used to compute the estimated cell values for the particular model selected, the method used to choose the model, and the criteria used to assess whether a particular model was satisfactory.

THE LOGARITHMIC MODEL

Birch (1) has described the usual linear model in the logarithmic scale for a three-dimensional contingency table. For ease of writing, the following description is also limited to three dimensions. For smoothing contingency tables, we have found that using at least four dimensions leads to more satisfactory fitting in the data on anesthetics. The method used here can be extended to the number of dimensions that seems to be appropriate for the size of the particular collection of data.

For a given linear model in the logarithmic scale, the same maximum likelihood estimates for the cell entries arise under a variety of sampling conditions. Nevertheless, for purposes of discussion we need to derive the distribution appropriate for our data. Let the subscript i refer to one of the I categories of variable 1, subscript j to one of the J categories of variable 2, and subscript k to one of the K categories of variable 3. Let x_{ijk} denote the number of observations (that is, the count) in cell (i,j,k) and $N = \sum_{i,j,k} x_{ijk}$.

In the present data only N, the total number of observations in the sample, is fixed. It is therefore convenient to think of the observations x_{ijk} as following the multinomial distribution. Cochran (4) reports that Fisher first gave a simple derivation of the multinomial under these conditions. If the observed x_{ijk} are regarded as following independent Poisson distributions with means y_{ijk}, their joint frequency function is:

$$\prod_{i,j,k} \frac{y_{ijk}^{x_{ijk}} e^{-y_{ijk}}}{x_{ijk}!}. \tag{1}$$

The total $N = \sum_{i,j,k} x_{ijk}$ also follows the Poisson distribution with mean $Y = \sum_{i,j,k} y_{ijk}$. The frequency function of N is therefore

$$\frac{Y^N e^{-Y}}{N!}. \tag{2}$$

The conditional distribution of the x_{ijk}, given that their total is N, is obtained by dividing expression 1 by expression 2. We then have the multinomial expressed in terms of probabilities, p_{ijk}:

$$\frac{N!}{\prod_{i,j,k} x_{ijk}!} \prod_{i,j,k} p_{ijk}^{x_{ijk}}, \tag{3}$$

where $p_{ijk} = y_{ijk}/Y$ and $\sum_{i,j,k} p_{ijk} = 1$.

Let us now define m_{ijk} as the expected cell value that would be obtained under the multinomial of expression 3. For fixed N we have $m_{ijk} = Np_{ijk}$, and so can substitute for p_{ijk} in expression 3. If we do this and take the logarithm (to the base e) of the likelihood, we have:

$$\log\left[\frac{N!}{\prod_{i,j,k} x_{ijk}!}\right] - \sum_{i,j,k} x_{ijk} \log N + \sum_{i,j,k} x_{ijk} \log m_{ijk}. \qquad (4)$$

The first two terms of this expression are unchanged, whatever the values of m_{ijk}. The last term, or "kernel," will change with m_{ijk}, and that is the part of the expression that is important in our development.

Having defined the distribution, we may now proceed to express the m_{ijk} in terms of a log-linear model. In Chapter IV-3 we introduced the u-term notation and described how individual u-terms can be regarded as representing simple or multiple-factor effects of the variables. We also showed that all subscripted u-terms are deviation scores, and hence sum to zero when added over one of the subscript variables. For the sake of completeness, we will recapitulate here.

Let us first write out the full three-dimensional model:

$$\begin{aligned}\log m_{ijk} = u &+ u_{1(i)} + u_{2(j)} + u_{3(k)} \\ &+ u_{12(ij)} + u_{23(jk)} + u_{13(ik)} \\ &+ u_{123(ijk)}. \end{aligned} \qquad (5)$$

The definitions of the u-terms are then as follows: over-all mean:

$$u = \sum_{i,j,k} \frac{\log m_{ijk}}{IJK};$$

main effect of variable 1 for category i:

$$u_{1(i)} = \sum_{j,k} \frac{\log m_{ijk}}{JK} - u;$$

two-factor effect between variables 1 and 2 for all cells at level i of variable 1, level j of variable 2:

$$u_{12(ij)} = \sum_{k} \frac{\log m_{ijk}}{K} - (u_{1(i)} + u_{2(j)} + u);$$

and similarly for the remaining terms. The consequence of the additive model is that, for the one-factor terms,

$$\sum_i u_{1(i)} = \sum_j u_{2(j)} = \sum_k u_{3(k)} = 0;$$

for the typical two-factor term involving variables 1 and 2,

$$\sum_i u_{12(ij)} = \sum_j u_{12(ij)} = 0,$$

and similarly for the other two-factor terms, $u_{13(ik)}$ and $u_{23(jk)}$. We also have for the three-factor term:

$$\sum_i u_{123(ijk)} = \sum_j u_{123(ijk)} = \sum_k u_{123(ijk)} = 0.$$

The complete model of expression 5 does not impose any further restrictions on the m_{ijk}. If we substitute this linear expression for log m_{ijk} in the log-likelihood of expression 4, we have:

$$\log \frac{N!}{\prod_{i,j,k} x_{ijk}!} - N \log N +$$

$$\sum_{i,j,k} x_{ijk} [u + u_{1(i)} + u_{2(j)} + u_{3(k)} + u_{12(ij)} + u_{23(jk)} + u_{13(ik)} + u_{123(ijk)}]. \quad (6)$$

Because the first two terms are independent of the u-parameters, they may be ignored. The remaining terms of expression 6 may be rewritten:

$$Nu + \sum_{i} x_{i++}(u_{1(i)}) + \sum_{j} x_{+j+}(u_{2(j)}) + \sum_{k} x_{++k}(u_{3(k)})$$

$$+ \sum_{i,j} x_{ij+}(u_{12(ij)}) + \sum_{i,k} x_{i+k}(u_{13(ik)}) + \sum_{j,k} x_{+jk}(u_{23(jk)})$$

$$+ \sum_{i,j,k} x_{ijk}(u_{123(ijk)}). \quad (7)$$

If, instead of a model with all possible effects, we define a model with, for instance, no three-factor effect, this would be equivalent to postulating that $u_{123(ijk)} = 0$ for all i,j,k, and the term $\sum_{i,j,k} x_{ijk}(u_{123(ijk)})$ would disappear from expression 7. Then the sufficient statistics for the remaining seven u-terms would be N, x_{i++}, x_{+j+}, x_{++k}, x_{ij+}, x_{i+k}, and x_{+jk}. These can all be derived from the three marginal face totals with typical elements x_{ij+}, x_{i+k}, and x_{+jk}. In other words, the kernel of the distribution no longer contains terms as detailed as x_{ijk}. It is this reduction of dimensionality that enables us to obtain more stable cell estimates with models that have only low-order u-terms. To fit such models to our observed x_{ijk}, we need some theoretical results. We will denote maximum likelihood estimates of the parameters by a prime; thus, u′ is the maximum likelihood estimate of u and m'_{ijk} is the maximum likelihood estimate of m_{ijk}. This distinction between theoretical values and maximum likelihood estimates, or "fitted" values, has not been made in Chapter IV-3.

The necessary theoretical results are given by Birch, who shows that for any reduced model:

(1) the marginal totals are maximum likelihood estimates of their expectations, for example, $x_{i++} = m'_{i++}$, which estimates m_{i++};

(2) there is only one set of u's, and hence m's, for which the likelihood function is a maximum; and

(3) the maximum likelihood estimates of the m's are determined uniquely by the appropriate marginal totals and the marginal totals are preserved.

In order to prove (2), Birch assumes that no cell is empty. This assumption is not met in our body of data; but consideration of the degrees of freedom involved leads to the conclusion that, if the appropriate marginal totals are not zero, they still provide a unique solution, regardless of whether the elementary cells are zero. Occasionally we have used a model when a marginal total was itself zero. In such a model, because our method preserves totals, no estimates different from zero can be derived for the expected cell entries for any of the empty cells whose sum is involved in the particular marginal entry. In effect, then, the number of independent equations to be solved simultaneously is reduced by one, and a unique solution is obtained for the remaining cells.

It should be noted that: (1) other methods can be developed that do not have the empty-cell limitation, and (2) when data come from several sources (institutions in this Study), the multinomial model may not apply and so the sufficiency cannot be counted on. Nevertheless, the idea of fitting in this manner can still be used without change.

To obtain the fitted m'_{ijk} in every cell for the model that involves the mean u, the three one-factor u's, and the three two-factor u's, the three configurations of two-dimensional face totals of x's are sufficient. The maximum likelihood estimates of the u-terms or of the m's are ordinarily derived iteratively. The need

for iteration occurs for this particular model only in three dimensions, but it occurs for most models of interest when the number of dimensions exceeds three. The method of iteration used in this study (to be described in the next section) produces the fitted m'_{ijk} without directly computing the u′-terms. Thus, although the u′-terms are a useful device from a theoretical point of view, and can readily be obtained from the m'_{ijk}, they are not needed in the calculations. They can be useful for purposes of interpretation, in that they give an analysis-of-variance summary of the data.

Nevertheless, for illustrative purposes we have computed the u′-terms for the low-death-rate operations (Table 1). This was a four-dimensional set of data and we fitted the same model to both deaths and estimated exposed. The model contained the mean u, the four main-effect terms, and the six two-factor terms. All higher-order terms were equated to zero.

Suppose we wish to find log $m'_{ijk\ell}$ ($i = j = k = \ell = 1$), the logarithm of the expected value of the first cell, the cell that is at level 1 of each of the four variables. We look at the u′-terms for the estimated exposed, and take the sum of the mean and the main-effect u-terms. These are:

$$u' + u'_{1(1)} + u'_{2(1)} + u'_{3(1)} + u'_{4(1)},$$

with values

$$5.5135 + 0.5078 + 0.2532 - 0.0538 + 1.1324 = 7.3531.$$

To these must be added the sum of the two-factor terms:

$$u'_{12(1,1)} + u'_{13(1,1)} + u'_{14(1,1)} + u'_{23(1,1)} + u'_{24(1,1)} + u'_{34(1,1)},$$

with values

$$-0.1442 - 0.0501 - 0.1716 - 0.2536 - 0.0960 + 0.4858 = -0.2297.$$

TABLE 1.--AN EXAMPLE OF u′-TERMS FOR LOW-DEATH-RATE OPERATIONS FITTED TO TWO-DIMENSIONAL FACES (AGENT, SEX, AGE, AND RISK)

[One-factor terms are vectors and have as many parameters as the variable has categories. Two-factor terms are two-dimensional matrices; the number of the column corresponds with the number of the category of the first variable, and the number of the row with the number of the category of the second variable.]

u′-TERMS FOR DEATHS					
Main u′-term: 0.7313					
One-factor u′-terms:					
u'_1	Agent 1	Agent 2	Agent 3	Agent 4	Agent 5
	0.4281	-0.2119	0.3047	-0.8157	0.2947
u'_2	Female	Male			
	0.0784	-0.0784			
u'_3	Age 0-9	Age 10-49	Age 50-69	Age 70+	
	-0.7419	0.0676	0.4689	0.2054	
u'_4	Risk U	Risk A1	Risk B1	Risk A2	Risk B2
	0.2321	0.8032	0.8609	-1.6676	-0.2287
Two-factor u′-terms:					
u'_{12}	-0.1086	0.0080	0.1478	0.0518	-0.0989
	0.1086	-0.0080	-0.1478	-0.0518	0.0989
u'_{13}	0.2037	-1.5580	-0.0929	1.0350	0.4121
	0.0111	0.2595	-0.0125	0.0041	-0.2622
	-0.1846	0.4876	-0.0690	-0.2659	0.0319
	-0.0302	0.8109	0.1743	-0.7732	-0.1818
u'_{14}	0.2799	-0.1391	0.1594	-0.2442	-0.0560
	0.1364	0.4586	-0.3991	0.2494	-0.4454
	0.1817	0.1855	-0.3129	0.0225	-0.0767
	-0.6519	-0.3009	0.2236	0.2844	0.4448
	0.0539	-0.2041	0.3291	-0.3121	0.1333
u'_{23}	0.0714	-0.0714			
	0.3367	-0.3367			
	-0.1024	0.1024			
	-0.3057	0.3057			
u'_{24}	0.0346	-0.0346			
	0.2931	-0.2931			
	0.0998	-0.0998			
	0.0048	-0.0048			
	-0.4324	0.4324			
u'_{34}	0.1692	-0.0654	-0.1915	0.0877	
	-0.0246	0.0087	0.2058	-0.1898	
	-0.0440	-0.0076	0.1096	-0.0580	
	-0.3479	-0.2301	0.3070	0.2711	
	0.2474	0.2945	-0.4309	-0.1110	

u′-TERMS FOR ESTIMATED EXPOSED					
Main u′-term: 5.5135					
One-factor u′-terms:					
u'_1	0.5078	0.1967	0.1927	-0.8230	-0.0742
u'_2	0.2532	-0.2532			
u'_3	-0.0538	1.1728	-0.0472	-1.0718	
u'_4	1.1324	2.7105	-0.1651	-1.5200	-2.1577
Two-factor u′-terms:					
u'_{12}	-0.1442	0.0391	0.2694	-0.0993	-0.0651
	0.1442	-0.0391	-0.2694	0.0993	0.0651
u'_{13}	-0.0501	-1.7774	-0.2755	1.1278	0.9752
	0.0026	0.4797	0.2701	-0.3013	-0.4512
	0.1333	0.6152	0.1706	-0.4659	-0.4533
	-0.0859	0.6825	-0.1652	-0.3606	-0.0708
u'_{14}	-0.1716	0.1574	-0.2448	-0.3780	-0.1191
	-0.1109	0.0290	-0.4257	0.5151	-0.0075
	0.0847	-0.0825	-0.3942	0.3922	-0.0001
	0.0794	0.2036	0.6685	-0.9698	-0.0184
	0.1184	-0.3074	0.3962	-0.3155	0.1083
u'_{23}	-0.2536	0.2536			
	0.3925	-0.3925			
	0.0090	-0.0090			
	-0.1480	0.1480			
u'_{24}	-0.0960	0.0960			
	-0.0672	0.0672			
	-0.0420	0.0420			
	0.2192	-0.2192			
	-0.0139	0.0139			
u'_{34}	0.4858	-0.2337	0.0832	-0.3353	
	0.3198	-0.0798	0.1986	-0.4385	
	-0.7014	-0.9278	0.5327	1.0965	
	0.6194	0.9647	-0.5173	-1.0667	
	-0.7235	0.2766	-0.2971	0.7440	

And the log m'_{ijkl} = 7.3531 - 0.2297 = 7.1234 (i = j = k = l = 1). The antilogarithm, 1241 (recall that base e was used), gives the fitted number of estimated exposed in this cell. This number is found in Table 6 of Chapter IV-3 on the line labeled "Fit EE" for agent 1, female, age 0-9, risk U.

If we were to compute the death rate in the customary way, as deaths/estimated exposed, the logarithm of the expected rate in a particular cell would be the difference between the logarithm of the expected value for deaths and the logarithm of the expected value for estimated exposed. Thus, the logarithm of the rate may be expressed as a linear combination of w-terms; dropping suffixes in parentheses, this is:

$$w + w_1 + w_2 + w_3 + w_4 + w_{12} + w_{13} + w_{14} + w_{23} + w_{24} + w_{34},$$

where

$$w = (u' \text{ for deaths}) - (u' \text{ for estimated exposed}),$$

$$w_{1(i)} = (u'_{1(i)} \text{ for deaths}) - (u'_{1(i)} \text{ for estimated exposed}),$$

and similarly for all w-terms. The w-terms have the same additive properties as the u-terms.

For the first variable, agent, the main effect w-term has parameter values as follows:

$$w_{1(1)} = 0.4281 - 0.5078 = -0.0797,$$

$$w_{1(2)} = -0.2119 - 0.1967 = -0.4086,$$

$$w_{1(3)} = 0.3047 - 0.1927 = 0.1120,$$

$$w_{1(4)} = -0.8157 + 0.8230 = 0.0073, \text{ and}$$

$$w_{1(5)} = 0.2947 - 0.0742 = 0.3689.$$

This orders the different agents in terms of their main effect. If the data could be fitted by a model that did not contain any w-terms involving variable 1, except the main effect w_1, then the ordering of the w_1 terms would correspond with the ordering of the over-all adjusted rates, however they were computed. In the present instance, the ordering of the w_1 terms is the same as the ordering of the adjusted rates given in Chapter IV-6, except for the interchange of agents 1 and 4. Our main purpose, however, is to obtain stable cell estimates, not over-all relationships.

If the method of fitting a log-linear model is to be effective in producing more stable cell estimates than would be obtained by using only observed cell values, then most of the variability between cells in the raw data should be described by the u-terms of lower order. In the three-dimensional case, for instance, it is theoretically possible, but unlikely, that the three-factor term u_{123} is large and the two-factor terms u_{12}, u_{23}, and u_{13} are small or nonexistent. Birch has postulated a "hierarchy" principle, and strictly speaking the methods used here are applicable only when such a principle holds. (Other methods could be developed.) The principle, as followed here, implies that, if a lower-order effect is zero, then all higher-order effects involving the same combination of variables are also zero.

In the three-dimensional case, we can think of the three-factor effect u_{123} as measuring differences in the two-factor effect u_{12} for each level of variable 3. The hierarchy principle states that, if $u_{12} = 0$ (that is, $u_{12(ij)} = 0$ for all values of i and j), then u_{123} must also be zero. The argument applies naturally to the other two two-factor effects as well. Thus, if a two-factor effect is on the average negligible, the principle implies that it is negligible for every level of the third variable.

When more than three dimensions are involved, the argument is extended to multifactor effects. In the four-dimensional case, if $u_{123} = 0$, then $u_{1234} = 0$. If $u_{12} = 0$, the four-dimensional model is reduced from a full complement of 16 u-terms down to 12 u-terms, because u_{123}, u_{124}, and u_{1234} are also zero. It may be shown that for s dimensions the total number of u-terms in the full model is 2^s. This is reduced by one-fourth to $3 \times 2^{s-2}$ if a two-factor effect is zero. One

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effect of this principle is to reduce greatly the possible number of models that could be fitted to a given set of data.

This principle does more. It defines groups of models for which the m-values may be obtained without iteration. These are referred to as "multiplicative" models. A special set of these models is called "simple multiplicative." These by definition have only one two-factor effect (and higher-order related terms) of zero; this definition holds for any number of dimensions. Because the m′-values are easily obtained for these models, they can be used in a first examination of the data to determine which of the iterative models is the most feasible to fit. This examination is described later (under "Selection of Model").

If we keep to the hierarchy principle, there is only one model that requires iterative fitting for three-dimensional data. This is the model that uses seven parameters, the only zero term being u_{123}. As soon as any other parameters are zero, we have a multiplicative model.

Let us consider the simple multiplicative model in three dimensions with $u_{13} = 0$ for all i, k. This model may be written:

$$\log m_{ijk} = u + u_{1(i)} + u_{2(j)} + u_{3(k)} + u_{12(ij)} + u_{23(jk)} . \qquad (8a)$$

It follows that

$$m_{ij+} = \sum_k \exp[u + u_{1(i)} + u_{2(j)} + u_{3(k)} + u_{12(ij)} + u_{23(jk)}]$$

$$= \exp[u + u_{1(i)} + u_{2(j)} + u_{12(ij)}] \sum_k \exp[u_{3(k)} + u_{23(jk)}], \qquad (8b)$$

and similarly:

$$m_{+jk} = \exp[u + u_{2(j)} + u_{3(k)} + u_{23(jk)}] \sum_i \exp[u_{1(i)} + u_{12(ij)}]. \qquad (8c)$$

We also have:

$$m_{+j+} = \exp[u + u_{2(j)}] \sum_i \sum_k \exp[u_{1(i)} + u_{3(k)} + u_{12(ij)} + u_{23(jk)}], \qquad (8d)$$

which may be written:

$$\exp[u + u_{2(j)}][\sum_i \exp(u_{1(i)} + u_{12(ij)})][\sum_k \exp(u_{3(k)} + u_{23(jk)})]. \qquad (8e)$$

From expressions 8a, 8b, 8c, and 8e, we find that

$$m_{ijk} = \frac{(m_{ij+})(m_{+jk})}{m_{+j+}}, \qquad (8f)$$

and so

$$m'_{ijk} = \frac{(x_{ij+})(x_{+jk})}{x_{+j+}} . \qquad (9)$$

These values of m'_{ijk} are the expected, or fitted, cell values for this model. Thus, when there is no two-factor effect between variables 1 and 3, to compute the m'_{ijk} we need the two two-dimensional faces with typical elements x_{ij+} and x_{+jk}. These are obtained by adding over the categories of variable 3 and over the categories of variable 1, respectively. We also need the one-dimensional margin with typical element x_{+j+}, obtained by adding over the categories of both the mutually independent variables 1 and 3. This margin could also be obtained from either of the faces. We will use the word "configuration" and capital X's to refer to any submatrix obtained by adding over the categories of one or more variables of the original matrix. In this language, for this model, the two configurations X_{ij+} and X_{+jk} are sufficient, because we can derive from them the configuration X_{+j+}.

If variable 2, say, has only one category, so that the suffix j may be dropped, then m'_{ik} may be estimated by

$$\frac{(x_{i+})(x_{+k})}{x_{++}},$$

or the product of the marginal totals divided by the grand total. Then expression 9 reduces to the familiar relationship commonly used in a two-way contingency table to obtain the expected value in each cell under the hypothesis of independence of row and column effects. Thus, in a two-way contingency table the test for independence is equivalent to setting up a linear model in the log-scale with three parameters, namely, the mean u and the two relevant one-dimensional u-terms, and comparing the results with the observed values. Expression 9 may be interpreted as an extension of this formula to the case of J two-way tables where variable 2 has J categories. In other words, the three-dimensional matrix may be regarded as J layers of two-way tables of size I×K, involving variables 1 and 3, the mutually independent variables.

FITTING THE MODEL BY THE ITERATIVE METHOD

Once a model has been selected, the fitted values in every cell are derived from the summary configurations. For illustrative purposes, discussion here centers again on a three-dimensional array of data for which the sufficient configurations are the three sets of two-dimensional face totals having typical elements x_{ij+}, x_{i+k}, and x_{+jk}. The dimensions of these faces are I×J, I×K, and J×K. We wish to obtain the fitted value m'_{ijk} for every cell. We will first describe the process and then give an example.

Step 1: Obtaining configurations. The data x_{ijk} are read into the computer and the three configurations of totals with typical cells, x_{ij+}, x_{i+k}, and x_{+jk} obtained. These totals are unaltered throughout the computation. When referring to the entire configurations we will use X_{ij+}, X_{i+k}, and X_{+jk}.

Step 2: Starting values. A constant is assigned to every cell of the m'_{ijk} matrix. In practice we used the value 1, thus $m_{ijk}^{(0)} = 1$, for all i, j, k. Every cell of this matrix is changed at every subsequent step. The superscript refers to the stage of iteration and indicates the current value of m'_{ijk}.

Step 3: Beginning the iteration. The m′-matrix is fitted to the first configuration, X_{ij+}. The procedure is multiplicative, thus

$$m_{ijk}^{(1)} = \left(\frac{x_{ij+}}{m_{ij+}^{(0)}}\right)\left(m_{ijk}^{(0)}\right) \text{ for all i, j, and k.}$$

Step 4: Continuation of the iteration. The m′-matrix is fitted to the second configuration, X_{i+k}, thus

$$m_{ijk}^{(2)} = \left(\frac{x_{i+k}}{m_{i+k}^{(1)}}\right)\left(m_{ijk}^{(1)}\right) \text{ for all i, j, and k.}$$

Step 5 and subsequent steps: The m′-matrix is similarly fitted to the third configuration, X_{+jk}. Then the cycle using the configuration of Step 3 is repeated. At the end of each cycle the amount of change that the last step has introduced is assessed. If the last step did not change any cell value by as much as 0.1, the procedure is terminated; otherwise, another cycle is performed. Suppose termination occurs after the rth cycle. Then the values of $m_{ijk}^{(3r)}$ are our approximation to the fitted cell values for this model, m'_{ijk}.

It can be shown that this process will always terminate (3). Discussion of speed of convergence must, of course, involve the criterion used for termination. Initially other criteria were tried. If the criteria were too strict, or involved more computation than comparing each cell difference with a constant value, the amount of machine-time required increased greatly. Inspection of intermediate values showed

that the criterion of a difference less than 0.1 for every cell was satisfactory. The intermediate values inspected were the sums of the absolute differences between the cells of the observed configurations being used and the corresponding values for the current m's. This was done at every step. The number of cycles involved in fitting various models is given in the final section of this appendix.

The program used was written in general terms so that any data matrix could be fitted to any selection of configurations of three dimensions or fewer. Provision was made for a data matrix of 3000 cells and as many as nine variables. Ten configurations could be incorporated, provided that none contained more than 100 cells. The program would also obtain the estimates for any multiplicative models in one cycle.

Example:

Suppose we have a 2×2×2 matrix and a sample of size 1214 distributed in the eight cells as follows:

Cell	x	Cell	x
1,1,1	213	1,1,2	527
2,1,1	27	2,1,2	198
1,2,1	60	1,2,2	48
2,2,1	22	2,2,2	119

We postulate $u_{123} = 0$ and proceed to fit the configurations X_{ij+}, X_{i+k}, and X_{+jk}. First we obtain these configurations:

X_{ij+}

	i=1	i=2
j=1	740	225
j=2	108	141

X_{i+k}

	i=1	i=2
k=1	273	49
k=2	575	317

X_{+jk}

	j=1	j=2
k=1	240	82
k=2	725	167

We initially put $m_{ijk}^{(0)} = 1$ for all i, j, and k, and then proceed to adjust the values of m′ by fitting each configuration in turn. The values after the first three fits and the final values after five cycles are given in Table 2. (The subscripts i, j, and k

TABLE 2.--EXAMPLE OF ITERATIVE FITTING

Cell	$m^{(0)}$	$m^{(1)}$	$m^{(2)}$	$m^{(3)}$	m'	F.T.*	x^2
1,1,1	1.0	370.0	238.23	213.06	218.90	-0.384	0.159
2,1,1	1.0	112.5	30.12	26.94	21.10	1.246	1.650
1,2,1	1.0	54.0	34.77	53.15	54.08	0.814	0.648
2,2,1	1.0	70.5	18.88	28.85	27.92	-1.128	1.255
1,1,2	1.0	370.0	501.77	522.19	521.07	0.270	0.068
2,1,2	1.0	112.5	194.88	202.81	203.93	-0.400	0.172
1,2,2	1.0	54.0	73.23	62.60	53.96	-0.797	0.658
2,2,2	1.0	70.5	122.12	104.40	113.04	0.575	0.314
Total		1214.00	1214.00	1214.00	1214.00	4.832	4.924

*Freeman-Tukey deviate; these are squared before they are added.

have been dropped from all column headings in the tables.) We also give two measures of goodness-of-fit between the m'_{ijk} and the x_{ijk}. These are the Freeman-Tukey deviate (defined below) and the usual squared deviate, $\chi^2 = (x-m')^2/m'$.

Turning to computational details to obtain the $m^{(1)}_{ijk}$, which are fitted to X_{ij+}, we add the $m^{(0)}_{ijk}$ over the categories of variable 3, for example,

$$m^{(0)}_{111} + m^{(0)}_{112} = m^{(0)}_{11+} = 2.$$

Then we adjust each of the terms forming this sum by multiplying by the ratio $x_{11+}/m^{(0)}_{11+}$, so we have

$$m^{(1)}_{111} = m^{(1)}_{112} = 1 \times \frac{740}{2} = 370.$$

To obtain the $m^{(2)}_{ijk}$, which are fitted to X_{i+k}, we add the $m^{(1)}_{ijk}$ over the categories of variable 2, for example,

$$m^{(1)}_{111} + m^{(1)}_{121} = m^{(1)}_{1+1} = 370 + 54 = 424,$$

and we get the ratio $x_{1+1}/m^{(1)}_{1+1} = 273/424$.

Then we have

$$m^{(2)}_{111} = m^{(1)}_{111} \times \frac{x_{1+1}}{m^{(1)}_{1+1}} = 370 \times \frac{273}{424} = 238.231$$

and

$$m^{(2)}_{121} = m^{(1)}_{121} \times \frac{x_{1+1}}{m^{(1)}_{1+1}} = 54 \times \frac{273}{424} = 34.769.$$

We proceed to fit X_{+jk} and then repeat the cycle until successive values for the same cell do not differ by more than 0.1. This example took five cycles, so we have taken the $m^{(15)}_{ijk}$ values to be our estimates of m'_{ijk}.

If we look at the sum of the squared Freeman-Tukey deviates and at the summed χ^2 deviates, we have the values of 4.832 and 4.924, respectively. Both measures are large for a χ^2 variable having one degree of freedom, but inspection of the pattern for individual cells shows that there is not any one cell where the fitted values depart extremely from the observed values.

Usually, we only have values of x_{ijk} and m'_{ijk}, and if they agree closely we accept the m'_{ijk} as giving more stable cell estimates. In the present example, the data are a random sample taken from a distribution for which the m_{ijk} were known. We show the construction of these theoretical m_{ijk} in Table 3. We set up a model with $u_{123} = 0$ but all other u-terms present, choosing the mean $u = 4.5$ so that the total sample size exceeded 1000. We summed the seven u-terms for each cell and took antilogarithms to give us the m_{ijk}. In Table 4 we compare the sample observations, x_{ijk}, and the fitted cell estimates, m'_{ijk}, with the theoretical values. We find the χ^2 value for the sample observations is 8.939 with seven degrees of freedom, but for the fitted estimates it is reduced to 4.081 with six degrees of freedom. Thus, in this example, our fitted values agree more closely with the theoretical values than with the observed values.

TABLE 3.--CONSTRUCTION OF MODEL WITH NO THREE-FACTOR INTERACTION

Cell	u_1	u_2	u_3	u_{12}	u_{13}	u_{23}	Log m for u = 4.5	m
1,1,1	0.4	0.5	-0.6	0.4	0.3	-0.2	5.3	200.337
2,1,1	-0.4	0.5	-0.6	-0.4	-0.3	-0.2	3.1	22.198
1,2,1	0.4	-0.5	-0.6	-0.4	0.3	0.2	3.9	49.402
2,2,1	-0.4	-0.5	-0.6	0.4	-0.3	0.2	3.3	27.113
1,1,2	0.4	0.5	0.6	0.4	-0.3	0.2	6.3	544.572
2,1,2	-0.4	0.5	0.6	-0.4	0.3	0.2	5.3	200.337
1,2,2	0.4	-0.5	0.6	-0.4	-0.3	-0.2	4.1	60.340
2,2,2	-0.4	-0.5	0.6	0.4	0.3	-0.2	4.7	109.947

TABLE 4.--COMPARISON OF SAMPLE VALUES AND FITTED VALUES WITH THEORETICAL VALUES

Cell	m	x	$\frac{(x-m)^2}{m}$	m′	$\frac{(m'-m)^2}{m}$
1,1,1	200.34	213	0.800	218.90	1.719
2,1,1	22.20	27	1.038	21.10	0.055
1,2,1	49.40	60	2.275	54.08	0.443
2,2,1	27.11	22	0.963	27.92	0.024
1,1,2	544.57	527	0.567	521.07	1.014
2,1,2	200.34	198	0.027	203.93	0.064
1,2,2	60.34	48	2.524	53.96	0.675
2,2,2	109.95	119	0.745	113.04	0.087
Total	1214.25		8.939		4.081

SELECTION OF MODEL

The selection of variables to be included and the numbers of categories per variable was largely an arbitrary process, based on discussion with anesthesiologists and inspection of the data. In general, the number of categories was kept as small as possible. Models were attempted that included differing numbers of variables. In the following discussion, the number of variables is s. If s was as small as 4, then it was sometimes found necessary to fit configurations of dimension as great as s-1. This could introduce too much random fluctuation of the raw data into the fitted values. If s was too large, then the total number of cells became large and the individual cell entries became very small, and each computed m′ depended on so many parameters that its error of estimation might be large.

We used simple multiplicative models to decide which u-terms seemed to be largest once the appropriate dimensions for a particular set of data had been fixed. We have derived the simple three-dimensional expression for m'_{ijk} when a single two-factor term is zero in expression 9. An expression of similar form exists for models of any dimension. Suppose, for example, we have five-dimensional data (the highest dimension we have used in this report). If $u_{12} = 0$ (and from the

hierarchy principle this implies that u_{123}, u_{124}, u_{125}, u_{1234}, u_{1235}, u_{1245}, and u_{12345} are also zero), then it may be shown that

$$m_{12345(ijklm)} = \frac{(m_{+2345(jklm)})\,(m_{1+345(iklm)})}{m_{++345(klm)}}.$$

Consequently, the two configurations X_{+2345} and X_{1+345} are sufficient. They are of dimension 4, and from them the third three-dimensional configuration that is needed, X_{++345}, may be obtained. In general, for s dimensions two configurations of dimension (s-1) are needed, and from them a third configuration of dimension (s-2) can be derived.

Initially, the models obtained by removing in turn each two-factor term and its higher-order relatives were investigated. For each model, simple multiplicative values for m′were computed for every cell. Then a measure of divergence between the observed x-value and the fitted m′-value was obtained for each cell. These measures were then summed to give a measure of deviation, which was compared with the appropriate degrees of freedom. We chose to look at simple multiplicative models first, to find out which effects were large.

By considering the example of expression 10 as consisting of many "layers" of a two-way table of variable 1 crossed with variable 2, it can be seen that each layer has (I-1) (J-1) degrees of freedom. Thus, if C is the total number of cells in the matrix, we have C/IJ layers. It may be shown that each layer is independent. Birch (2) has shown this for three dimensions. The independence means that we can add the degrees of freedom for each layer. Thus, the degrees of freedom for this simple multiplicative model are C(I-1)(J-1)/IJ, provided that there are no empty cells in the (s-1)-dimensional matrices. The measure of deviation obtained when u_{12} and its relatives were equated to zero was compared with this number of degrees of freedom.

This fitting of a simple multiplicative model was repeated for each two-factor u-term, and the discrepancy between the measure of deviation and the degrees of freedom was obtained for each. When the measure of deviation was small relative to the degrees of freedom, the two-factor term would ordinarily not be included in the iterative model to be fitted later. Because interest was focused primarily on the effect of agent in this Study, the two-factor effects involving agent were always included, regardless of the relative size of the measure of deviation. All other two-factor terms that were associated with relatively large measures of deviation were included.

For each set of data, all the possible $\binom{s}{2}$ simple multiplicative models of this type were fitted. If several of these models showed small measures of deviation relative to the degrees of freedom, the two-factor terms that were equated to zero in these models were considered to be unimportant. The next procedure was to fit a model that included only the important two-factor terms, in addition to the s one-factor terms and the mean u-term. Usually, this model required iterative fitting. When it had been fitted, a measure of deviation and degrees of freedom were again computed. On the basis of these, a decision was made either to use this model for final presentation or to try fitting a different model.

If none of the simple multiplicative models gave relatively small measures of deviation, the first iterative model attempted included all the two-factor effects. If this did not fit the data well, we proceeded to models that included three-factor effects. Effects of higher order than three were never used in this study. When it was necessary to include three-factor effects, they were all included. It is possible that prolonged search would have detected other models that fitted the data as well as those we used, or even better. We were concerned not with finding the optimum model, but with finding a model that fitted the data adequately and provided more stable cell estimates than the original observations themselves. In doing this, it is well if the number of cells in the configuration to be fitted is kept as small as possible.

Throughout this section the term "measures of deviation" has been used as a means of assessing how well the model fitted the data. The reason for this circumlocution is that at various times we used three such measures. In some of the preliminary investigations, χ^2 was used, although it was realized that it might be a

poor choice for small cells. When the final models were to be fitted, John Tukey suggested a convenient measure and it was used throughout this study. This measure, referred to as the "Freeman-Tukey deviate," (5) is defined as follows. If x is the observed count in a cell and m′ the fitted value, the deviate for this cell is:

$$d = \sqrt{x} + \sqrt{x+1} - \sqrt{4m' + 1}.$$

The transformation to $\sqrt{x} + \sqrt{x+1}$ is known to aid stabilization of variance. The asymptotic value of the mean of these transformed variates is $\sqrt{4m' + 1}$ for large m′. The deviate is approximately distributed according to the standard normal. The sum of squares of these deviates may be regarded as a χ^2 measure with the appropriate degrees of freedom for the data on deaths.

It is more difficult to assess how well the model fits the data on estimated exposed. To get an estimate of the numbers exposed, each observation in the random sample of operations was weighted by the sampling ratio for the particular institution from which the observation was drawn. This weighting had to be done before the model was fitted. When measures of deviation were computed in the manner just described for the death data, the estimates were always much larger than the related degrees of freedom, as would be expected, inasmuch as the weights were much larger than unity. The measures could be reduced to values more nearly resembling the usual χ^2 by dividing by the average weighting factor. We have done this in Table 5 and find that, although the measures are much closer, they are still large, relative to the measures obtained by fitting deaths. Greater reduction is achieved if, instead of using the arithmetic average of the weighting factors, we divide by the square root of the average squared weighting factor. We could obtain further refinement by taking into account differences in total numbers of observations between institutions.

To justify any of these average factors, rather broad assumptions about differences in distributions between institutions are needed. Instead of attempting to determine the most desirable factor, we checked, by using a different approach, that the large measures of deviation observed were indeed due to the weighting. For some sets of data, we fitted the same model to the cases before they were weighted. We found that the measures of deviation then obtained were comparable with those obtained for the deaths. Because there is no reason to suppose that the weighted data would exhibit multiple-factor effects not shown by the unweighted data, we were satisfied that our measures of deviation were not unduly large.

Apart from providing an over-all measure, the computation of deviates served a better purpose. In every instance in which a model was fitted, the Freeman-Tukey deviates were printed out for every cell. These were then inspected to ensure that their distribution was compatible with what would be expected from random fluctuations.

DETAILS OF MODELS USED IN THIS STUDY

This section discusses some of the models fitted in this study in some detail. The discussion covers models selected for display in this report, that is, the models that we believed gave the most satisfactory fit for each particular set of data, and covers some models which we fitted but have not displayed.

Details of the models discussed are given in Table 5. For each set of data, the description of the model is followed by values of Σd^2 for deaths and estimated exposed. As explained in the preceding section, the measure of deviation is large for the estimated exposed because every observation was weighted. We have divided the measure by the average weighting factor and this number appears directly below the uncorrected value in brackets. This average weighting factor is an underestimate of the additional amount of variability introduced, and so the corrected value is still large but much closer to the value obtained for the deaths. The next column, labeled "d.f.," shows the number of degrees of freedom with which Σd^2 should be compared. The last column gives the number of cycles to convergence. All models required iterative fitting.

The expression Σd^2 refers to the sum of squares of the Freeman-Tukey deviate. The degrees of freedom were computed by counting the number of non-empty cells in the fitted model and subtracting from it the number of independent parameters fitted. Thus, because of zeros, even though the same model is presented for both deaths and estimated exposed, the number of degrees of freedom

TABLE 5.--MEASURES OF DEVIATIONS FOR SELECTED MODELS

Data set	No. of variables	Model		Σd^2	d.f.	Cycles
Low	4	All 6	D	144	136	3
		2-dimensional faces	EE	10422	136	8
				(443)		
	4	All 4	D	51	33	7
		3-dimensional faces	EE	1578	44	8
				(67)		
Mid	5	All 10	D	482	447	3
		3-dimensional faces	EE	15540	418	5
				(711)		
	4	All 4	D	167	141	3
		3-dimensional faces	EE	4767	130	7
				(218)		
High	4	All 6	D	562	243	8
		2-dimensional faces (including agent but not sex)	EE	7846	213	10
				(365)		
	4	All 6	D	96	81	5
		2-dimensional faces (without agent)	EE	2867	74	6
				(133)		
Chole	6	A selection of 8 from 15 possible 2-dimensional faces	D	384	483	2
			EE	16800	483	4
				(743)		
	5	The corresponding 7 2-dimensional faces (10 possible)	D	182	218	2
			EE	9012	218	4
				(398)		

may differ slightly. We use the abbreviations "Low," "Mid," and "High" for the low-death-rate, middle-death-rate, and high-death-rate sets of data, and "Chole" for cholecystectomies. Details of the variables involved and numbers of cells are given in Tables 3 and 5 of Chapter IV-3. We turn now to Table 5 of this appendix.

The first models listed in Table 5 were fitted to the low-death-rate operations. For the low-death-rate operations, one advantage of fitting to two-dimensional faces, compared with three-dimensional configurations, is seen from the relative magnitude of the deviations: for the deaths, the former gives a χ^2 value of 144 with 136 degrees of freedom, whereas the latter gives 51 with 33 degrees of freedom. Another reason for preferring the former model is that fitting to three-dimensional configurations involves 14 empty cells among the fitted configurations for the estimated exposed, whereas the two-dimensional model involves none.

For the middle-death-rate operations, which are listed next, there seems to be little basis for choosing between four and five variables if the goodness-of-fit is considered. Use of four variables yields fewer empty cells.

For the high-death-rate operations, it is difficult to fit a model to a multi-dimensional contingency table that includes both agent and operation as variables. A reason is that, for one of the four operation codes, the sample of operations did not include any observations where ether was used, and for another operation code, hardly any where cyclopropane was used. Yet it would be unsatisfactory to amalgamate the four operation codes, because their death rates vary considerably.

To overcome the empty-cell difficulties and permit agent-specific estimates, an additional device was introduced. Constants were added to every cell before fitting and subsequently removed from the expected values. For the estimated exposed, the constant chosen was 40, approximately equivalent to two more observations per cell before weighting. For the deaths, the constant was 4; 4/40 = 10 percent, approximately equal to the over-all death rate for these operations. Although

the 10 percent ratio seems reasonable, the choice of 4 and 40 is somewhat arbitrary and more work is needed to determine either the wise selection of constants or alternative methods. These ideas are suggested by Bayesian estimation in multinomial problems. The deviations for this model with added constants are not given in Table 5. The model given shows why the device was necessary; the fit obtained from two-dimensional faces is poor and the number of cycles to convergence is greater than for any of the other models fitted.

In addition to this model, which includes the variables agent, operation, risk, and age, we also fitted another model to the high-death-rate operations where the variable agent was omitted but the variable sex was introduced. We provided a fitting exclusive of agent because physicians may be interested in the death rates for particular categories of patient, regardless of the anesthetic used. We see that for this model the irregularity of the data is not as great and a satisfactory fit was obtained from the two-dimensional faces.

The cholecystectomies were originally fitted to six variables. The sixth variable, "period," was a dichotomy in which each category represented 2 years of observations. With this large number of variables, it was enough to include a selection of the faces. In the second model listed, the variable period was removed, reducing the number of variables to five. When the same combinations of the remaining variables were fitted, the sums of deviations were relatively closer to the value expected for the degrees of freedom, but still smaller than this value. This is the model presented in Chapter IV-3.

To summarize, Table 5 shows for the low-death-rate data two models of differing dimensions fitted to the same set of data and the reasons for preferring one over the other. For the middle-death-rate data, we show the same dimension of model fitted to differing numbers of variables, and there is not much difference between their goodness-of-fit. For the high-death-rate data, we show two examples where the same dimension of model was fitted to the same number of variables but a different selection; here one model is satisfactory, but the other is a very poor fit. For the cholecystectomy data, we show two examples where a good fit was obtained from a selection among the possible two-dimensional faces, instead of using the total number available.

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Abstract of Chapter IV-4

Smear-and-sweep is a procedure for aggregating sparse multidimensional contingency tables by repeatedly spreading out the data into a two-way classification (of which one variable, except at the first stage, is the conglomerate variable formed at the preceding stage), and then pooling the resulting cells according to their ordering on "death rate" to produce categories of a new conglomerate variable ready for the next stage. The final conglomerate variable defines a small number of categories that are more-or-less homogeneous with respect to death rate and that allow, in part, for the effects of all the variables and their interactions; such categories form a basis for calculating comparative standardized death rates.

A process like this is subject to questions regarding many of the choices involved, e.g., the order in which the variables are introduced and the method of estimating within-cell death rates to be used in pooling. In applying smear-and-sweep to the middle-death-rate operations in the National Halothane Study, many choices were tried; this chapter presents and compares the results.

To eliminate ratio estimator bias and obtain confidence limits for the interagent death-rate differences, the standardized death rates are jackknifed over institutions. The resulting tables of pseudo-values of death rate by agent, population, and institution are carefully examined by standard (e.g., ANOVA) and nonstandard (e.g., robust location estimation) techniques.

The conclusions reached correspond to those found by other approaches: halothane and nitrous oxide-barbiturate are assigned death rates of about 2 percent; cyclopropane and Other appear measurably higher, with death rates of about 2½ percent; the difference in death rate between these groups is statistically significant (at 5 percent) when examined in the most sensitive way; the death rate for ether looks low but is too ill-determined to yield definite comparisons.

CHAPTER IV-4. THE SMEAR-AND-SWEEP ANALYSIS

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WHAT SMEAR-AND-SWEEP IS

The large number of variables available in the National Halothane Study produces such a multiplicity of cells in the complete cross-classification that, as has been noted, the data are too sparse for cell death rates to be interpreted individually. One way to handle this situation is to limit ourselves to questions that may be answered in terms of summary statistics, such as standardized death rates (by contrast, for example, with procedures designed to fit, and directly interpret, detailed models). Our problem is then to compute versions of these

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summary statistics that will have most of the advantages of control on all the known and available interfering variables.

We must state the problem this way for three reasons: (1) data are so dilute that direct control on all the available variables is almost as impractical as direct interpretation of the cross-classified data; (2) variables that are not available (that may not even have been thought of) may have such important influences that their control would be most desirable; and (3) the available control variables are given in broad groups and involve classification error and attenuation. The second and third considerations are not peculiar to this Study; in fact, with respect to them, the data in this Study are more adequate than usual.

Smear-and-sweep is a form of analysis that attempts to pool the cells of the cross-classification into categories in which the death rates (averaged over agents) are reasonably similar, and then calculates standardized death rates based on those categories. In all such methods, category formation is a qualitative analogue of index formation, and standardization provides control in a way analogous to the common use of stratified sampling.

Smear-and-sweep differs from the other methods of this class in its ability to bring in many more control variables than can be used simultaneously in methods that do not assume a specific functional form. It does this by working with two variables at a time, one being (except at the initial step) the categorization obtained in the previous step. Categories must be formed in a way that adequately avoids the (direct) effects of the particular anesthetic agent used, because those effects will almost certainly not be balanced across the cells defined by the control variables. To ensure this, the selection of categories must be based on all the relevant data in such a way that the name of the anesthetic used has no direct effect. On the null hypothesis, anesthetic has no effect; hence, it could have no effect in the category formation, and finding a significant effect in the death-rate analysis gives solid evidence against the null hypothesis--indeed, it gives solid evidence as to the direction of the major differences. (The estimation of the amount of the differences, which is not our concern here, raises some difficulties, which are commented on in Appendix 3.)

The advantage of this approach is that it readily permits us to handle complicated bodies of data that would otherwise require nonlinear models or high-order interactions.

In use, smear-and-sweep requires many choices, not only as to the variables included and the order in which they are considered, but as to general frameworks and the many details involved in providing cell "death rates" and using them to determine how the cells are to be combined into categories. Moreover, because the grouping must be on the basis of the observed data, the category into which a particular cell is pooled is influenced by sampling fluctuations, through their effect on cell "death rates."

We might observe here that an analysis of the data as a stratified sample can be carried out directly, provided that the categories to be used can be determined a priori. The study of shock, presented in Chapter IV-7, is such an analysis. The distinction between that approach and smear-and-sweep is that the categories used in the latter are selected to try to make the death rates within each category about the same, rather than to give the categories any intrinsic medical meaning. Death rates can be estimated only after the data have been observed; hence, these categories must be formed a posteriori.

To avoid spreading the data too thinly, we proceed sequentially, "smearing" the data out onto the cross-classification of two variables, then "sweeping" them up into categories of approximately equal numbers of deaths. These categories then form the levels of a composite variable. We then take the third variable on which we wish to control, and smear the data out onto the cross-classification of this third variable with the composite variable just formed. This procedure is continued, smearing and sweeping repeatedly until we have introduced all the variables on which (or on suitable combinations of which) we are to control.

Once the final set of categories has been chosen, we may compute standardized death rates over them, corresponding to various populations. These standardized rates are weighted averages of the death rates associated with a particular agent in each category, the weights being the fractions of the given population in that category. The standardized rates may be thought of (subject to issues to be discussed later) as the death rates one might expect if the agent in question were applied to the given population. We choose this direct standardization because we feel that it is easier to interpret than indirect standardization. If the categories are not too small, there is essentially no difference between direct and indirect standardization. We want an over-all comparison of the agents and a comparison for some special populations. We want an error term, so that we can test whether differences between the standardized death rates for the various agents are real or might reasonably be attributed to random error. The relevant error term would appear to be the comparison across hospitals, inasmuch as we would like the conclusions of this analysis to apply to hospitals other than those in the National Halothane Study. Hospital main effects (differential death rates not accounted for by standardization) must be removed, however, because they are known to exist and to be large enough to swamp the effects we are looking for.

We may obtain such an error term and provide what may be thought of as an adjusted estimate for each hospital by a procedure known as "jackknifing," which is discussed later.

To summarize, smear-and-sweep analysis is a technique for grouping data into categories (sequentially introducing each interfering variable), then estimating various standardized death rates over these categories and jackknifing the estimates to obtain "pseudo-values" of the death rates for each hospital, so that we may compare the anesthetics.

HOW TO USE SMEAR-AND-SWEEP

This section describes the implementation of the general technique presented in the last section. Several parameters will appear; we make no attempt to specify them at this point, but they will be considered again, after we have looked at some results of applying the technique to the data of the National Halothane Study.

The smear-and-sweep analysis has three distinct parts: forming the categories, estimating standardized death rates, and comparing the standardized rates.

As outlined above, the conglomeration process that produces the categories is carried out sequentially. The parameters include the order in which the interfering variables are introduced and the number of the available variables to be used. Anesthetic agent, as noted above, is to be completely ignored in this step.

Once we have chosen two variables, and smeared the data into the cells of that two-way cross-classification, we must estimate the average death rate in each cell. We are tempted to use only the data in an individual cell and thus make the pooling wholly data-directed, i.e., independent of any assumed regularity. However, because of the small numbers of observations that may appear in the cells, it is better to borrow strength from a smoothed estimate by using an estimator of the form

$$\hat{p} = \frac{D+Mp'}{EE+M} ,$$

where

D and EE are, respectively, the numbers of deaths and estimated exposed in the cell;

p′ is a smoothed estimate of the death rate in the cell, in this instance obtained from an additive model fitted by least squares to a table whose entries are a suitable function of the crude death rates (D/EE); and

M is a constant that may be interpreted as the number of EE that we feel the estimate p′ is worth, in terms of the smallness of its variability.

The value of M and the function of crude death rate to be used in obtaining p′ are operating parameters, which must be selected.

Having estimated the average death rate in each cell, we must pool the cells into categories. This is done by listing the cells in order of increasing death rate, and dividing the list into segments containing approximately equal numbers of deaths; each segment becomes a category. Other rules for sweeping are possible, such as a modified ordering, or division of the list into segments containing equal numbers of estimated exposed or equal variances of estimated death rates. Even with the method used, we must choose the size of the categories. In practice, this size was fixed in terms of a minimum number of deaths per category; other choices are possible.

For any set of choices of the parameters, the categories may now be determined. The next step is to calculate the standardized death rates. As mentioned earlier, the standardized death rate is the sum over all categories, of the products of death rate by population proportion. The death rate associated with an agent in a particular category is simply estimated as the ratio of the number of patients receiving the agent who died to the estimated number exposed to the agent (or 1, if that ratio exceeds 1). The fraction in each category of the population of patients exposed to a given agent is estimated by the corresponding fraction observed, based on the total estimated number exposed to the agent.

We compute the standardized death rate for each agent, first with respect to the over-all population, and second with respect to the characteristic population to which each of the other agents is normally applied.

These standardized death rates are now jackknifed. This is a technique due to Quenouille and Tukey for estimating variance and removing any 1/N bias, such as is present in ratio estimators like death rates (1,3-5). (Because the hospitals, which we use as blocks, are not of equal size, the leading term in the bias is not completely eliminated, but may be shown to be less than 2 percent of its previous size; see Appendix 1.) Briefly, jackknifing is a technique for use with nonlinear statistical estimators, whereby the data are divided into B blocks, and then the B quantities (called "pseudo-values"),

$$B \times \left\{\begin{matrix}\text{estimate computed}\\ \text{from all the data}\end{matrix}\right\} - (B-1) \times \left\{\begin{matrix}\text{estimate computed from all the}\\ \text{data except that in the ith block}\end{matrix}\right\} ,$$

are formed. The mean of the pseudo-values is a new estimator, unbiased at order 1/N; and 1/B times the variance of the pseudo-values is an estimate of the variance of this new estimator. The pseudo-values themselves may be regarded

for some purposes, including the application of certain significance tests, as approximately independent replications of the original estimator.

Thus, it is these jackknifed standardized death rates that we shall see in the next section. Before we look at them, however, we should give some thought to how the comparisons should be carried out.

The most naive approach is to observe that for each agent-population combination, we have 34 pseudo-values; and hence we can estimate a mean and standard deviation. These enable us to compare the means. This approach is fine for a start, in that it gives a crude interval, but if we attempt to ask too delicate a question, we find that it is inadequate. It fails in two ways: (1) no account is taken of the effects of differences between hospitals, which are large enough to swamp the differences that we are looking for; and (2) means and variances are always badly affected by outliers or long-tailed distributions, and the death-rate data are very long-tailed.

The most obvious way to cure the first failing is to use analysis of variance on the table of pseudo-values, removing the hospital main effects. This approach is still sensitive to the outlier problem, however, and in addition we have another problem. As we will see, it seems unreasonable to assume homogeneity of variance: death rates associated with ether are not as well determined as the others. If we remove outliers and repeat the analysis with and without ether rates, the comparison of the resulting analyses of variance will be instructive.

Another way to cure the failings of the naive technique is to use a nonparametric procedure. Ranova, or analysis of variance of ranks, removes hospital effects by doing the ranking within hospital, and ranks are insensitive to numeric values of outliers. Unfortunately, this technique lacks power and has the disadvantage of not giving estimated death rates.

The final method we use is simultaneous comparison between all pairs of the agents. This analysis, like the ranova, is carried out only on the 34×5 table of pseudo-values of over-all death rate. We regard its rows as 34 observations of a five-dimensional vector, and estimate a mean vector and covariance matrix. This permits us to make simultaneous comparisons of all agent-agent differences without assuming any special form for the correlation between the observations, or any specific ratios between variances, while canceling out hospital main effects. If, instead of a mean vector and covariance matrix, we use a robust multivariate location procedure, obtained by least pth deviations (2), this approach is not sensitive to outliers.

One last tool that we will mention is a criterion for comparing choices of parameters. We take logarithms of each entry in the 5×5 table of pseudo-value means for anesthetic agent vs. population. A simple additive model with agent and population main effects is fitted, and the residual sum of squares is then used as our criterion. Because we would like statements about populations and agents to be independent, small values of the criterion are desirable. Why do we choose this particular criterion? Other than the interaction term interpretation just mentioned, we may view the residual sum of squares as a measure of error in approximating the 5×5 table that is a function of 10 vectors by a simpler 5×5 table that is merely a function of nine scalars. The preliminary logarithmic transformation seems sensible, both intuitively and from inspection of the data. Moreover, for many of the parameters of the smear-and-sweep that can be selected by ad hoc arguments, this criterion yields the same choice. These may not seem very telling arguments, but fortunately the final results are so similar that the choice of the parameter-determining criterion is not critical.

RESULTS

Various combinations of parameters were tried on the middle-death-rate operations and are available for comparison. They are listed in Table 1. Broadly, the results are the same for all these cases. For example, consider the death rates by agent, standardized to the over-all population, as given in Table 2.

We see that, regardless of the parameters chosen in the smear-and-sweep, the standardized death rate associated with halothane is similar to that for nitrous oxide-barbiturate, at about 2.0 percent. The death rate associated with Other is noticeably higher, at about 2.4 percent, and that with cyclopropane higher yet, at about 2.5 percent. The analyses for ether, however, behave erratically, the standardized death rate appearing to change wildly with the parameters. This may be traced directly to the infrequent use of ether in operations with higher death rates. Hence, there are exceedingly few cases in the random sample, and it makes a large difference which category they fall into.

We might wish to inquire whether the differences observed in Table 2 are statistically significant. Our first approach is to consider the variance of the pseudo-values corresponding to each entry in the table; from these we can calculate a standard error for each. These standard errors are given in Table 3.

The remarkable agreement in the columns of Table 3 again indicates that the choice of the various parameters in smear-and-sweep analysis is not as important as might have been feared. Notice also the large difference between the standard error of the ether death rate and any of the others. This is not surprising: ether is used much less than the other agents, and so we might have expected its death rate to be poorly determined.

Although these standard errors are useful in that they show the degree of precision of our

TABLE 1.--ANALYSES PERFORMED

Analysis	Variables* (in order)	Transformation**	M***	No. of categories	Criterion
I	OAR	SQRT	5000	24	0.0164
II	OAR	SQRT	5000	12	0.0214
III	OAR	SQRT	500	25	0.0943
IV	ORA	LN	5000	24	0.0508
V	ORA	SQRT	5000	24	0.0138
VI	ORA	SQRT	500	24	0.0392
VII	ORA	SQRT	50	24	0.0365
VIII	ARO	SQRT	500	25	0.0132
IX	ORAL	SQRT	500	24	0.0755
X	OARL	SQRT	500	24	0.0257
XI	LOAR	SQRT	500	24	0.0405
XII	LORA	SQRT	500	24	0.0249

*O = operation, A = age, R = risk (physical status), and L = length (duration) of anesthesia. O and L themselves have been grouped to reduce the number of levels.
**SQRT = square root; LN = natural logarithm.
***A constant that weights the death rate observed in the cell.

TABLE 2.--OVER-ALL DEATH RATES FOR MIDDLE-DEATH-RATE OPERATIONS ESTIMATED BY VARIOUS ANALYSES

Analysis	Agent				
	H	N-B	C	E	O
I	0.0193	0.0202	0.0253	0.0179	0.0241
II	0.0186	0.0201	0.0259	0.0165	0.0255
III	0.0191	0.0203	0.0250	0.0247	0.0249
IV	0.0209	0.0199	0.0255	0.0200	0.0250
V	0.0203	0.0205	0.0255	0.0183	0.0245
VI	0.0208	0.0212	0.0245	0.0209	0.0241
VII	0.0214	0.0213	0.0264	0.0163	0.0243
VIII	0.0192	0.0199	0.0254	0.0181	0.0241
IX	0.0215	0.0207	0.0253	0.0195	0.0241
X	0.0199	0.0212	0.0254	0.0186	0.0269
XI	0.0195	0.0219	0.0250	0.0214	0.0238
XII	0.0197	0.0210	0.0254	0.0190	0.0240
range	0.0029	0.0020	0.0019	0.0084	0.0031

TABLE 3.--STANDARD ERRORS OF ENTRIES IN TABLE 2

Analysis	Agent				
	H	N-B	C	E	O
I	0.0028	0.0018	0.0016	0.0051	0.0024
II	0.0035	0.0016	0.0015	0.0052	0.0024
III	0.0027	0.0016	0.0016	0.0053	0.0018
IV	0.0021	0.0016	0.0017	0.0039	0.0022
V	0.0029	0.0016	0.0016	0.0038	0.0022
VI	0.0017	0.0019	0.0016	0.0030	0.0022
VII	0.0018	0.0013	0.0017	0.0049	0.0021
VIII	0.0027	0.0018	0.0017	0.0048	0.0020
IX	0.0019	0.0016	0.0016	0.0060	0.0019
X	0.0021	0.0018	0.0014	0.0043	0.0019
XI	0.0025	0.0018	0.0014	0.0044	0.0020
XII	0.0025	0.0014	0.0015	0.0040	0.0018

death-rate estimates, they have two serious defects: they do not take account of hospital main effects, and they are sensitive to outliers. The former is not completely undesirable, for it enables us to consider the question: "To what extent can we detect differences between the agents if we ignore differences between hospitals?" That question concerns not only the error variance, but also the relative magnitudes of the hospital and agent main effects. We are led to the answer that, ignoring the effect of outliers, we are not able to detect any differences. As we shall see, this is due both to outliers and to hospital effects.

We may go on to ask the question: "Taking into account the hospital main effects, can we detect differences between agents?" We naturally are tempted to apply ANOVA to the 34×5 table of pseudo-values of over-all death rates for hospital vs. agent. We will illustrate, using only analysis VIII (in which we standardized on age, risk, and operation in the order ARO, fitted p' using a square root transform with M = 500, and used 25 categories); results for other analyses are similar.

The table of pseudo-values for this case appears as Appendix 4. Negative death rates, such as appear there, should not disturb us. These are pseudo-values, and if small ratios are to be unbiased, occasional negative numbers must be expected. Proceeding in a straightforward manner to compute an analysis of variance, we produce Table 4.

Because the F ratio for agent effects is less than its critical value, we might be tempted to conclude that there was no significant agent effect. Before jumping to such a conclusion, however, we should observe the lack of homogeneity in the variances, and also observe that over two-thirds of the error sum of squares comes from four residuals defined by hospital-agent pairs (9,E), (11,E), (8,H), and (20,E), three of which involve ether. We feel compelled to repeat the analysis, leaving out ether; doing this gives Table 5.

We see that both the effects are now significant, although the residual (8,H) still contributes 40 percent of the error sum of squares. Trimming this outlier, if appropriate, would increase both F ratios.

Another way to carry out these tests is by ranova. Here we rank the death rates for each hospital, then sum the ranks for each agent. The statistic

$$W = \frac{12}{nk(k+1)} \Sigma R_i^2 - 3n(k+1),$$

where

k = number of items being ranked,

n = number of times we rank, and

R_i = sum of ranks for ith item,

is approximately χ^2_{k-1}.

In our case the sums of the ranks are:

H	N-B	C	E	O
81	83	121	109	116

for a W of 16.56 on four d.f., which is significant at the 0.5 percent point.

The last way we will consider the table of death rates cross-classified by agent and hospital is to make multiple comparisons by establishing simultaneous confidence intervals on the difference in death rates between each pair of agents. From the five-dimensional mean and variance matrix, we get direct estimates of these pairwise differences and their variances; additive hospital effects do not enter, nor variances

for other agents. However, with only 33 degrees of freedom, the analysis is very susceptible to outliers, so that when we first attempt it, we obtain Table 6, in which none of the differences is significant because all the intervals include zero.

However, if we decide to use the more robust estimators obtained by minimizing pth deviations for $p < 2$, we obtain Table 7 for $p = 1.5$ and Table 8 for $p = 1.25$. The asterisks indicate the significant differences H - C, H - O, and N-B - C. Notice that the robust estimators both gave about the same intervals, and that the intervals are only about half as long as those of the least squares method, indicating how badly the outliers had increased the variance estimates appropriate to simple arithmetic means.

TABLE 4.--TWO-WAY ANALYSIS OF VARIANCE

	Sum of squares	d.f.	Mean square	F	5% critical value
Hospitals	0.01553	33	0.000471	2.06	1.55
Agents	0.00138	4	0.000346	1.50	2.44
Error	0.03026	132	0.000229		

TABLE 5.--TWO-WAY ANALYSIS OF VARIANCE WITHOUT ETHER

	Sum of squares	d.f.	Mean square	F	5% critical value
Hospitals	0.008997	33	0.000273	2.56	1.57
Agents	0.000941	3	0.000314	2.94	2.70
Error	0.01058	99	0.000107		

TABLE 6.--DEATH-RATE ESTIMATES BASED ON LEAST SQUARED DEVIATIONS

H	N-B	C	E	O
0.0192	0.0199	0.0254	0.0181	0.0241

5% simultaneous intervals for differences

H - N-B	(-0.0105, 0.0090)
H - C	(-0.0149, 0.0026)
H - E	(-0.0142, 0.0164)
H - O	(-0.0112, 0.0014)
N-B - C	(-0.0121, 0.0012)
N-B - E	(-0.0146, 0.0182)
N-B - O	(-0.0112, 0.0029)
C - E	(-0.0066, 0.0210)
C - O	(-0.0047, 0.0072)
E - O	(-0.0196, 0.0076)

TABLE 7.--DEATH-RATE ESTIMATES BASED ON LEAST 1.5 POWER DEVIATIONS

H	N-B	C	E	O
0.0201	0.0195	0.0256	0.0217	0.0247

5% simultaneous intervals for differences

H - N-B	(-0.0057, 0.0068)
H - C	(-0.0106, -0.0003)*
H - E	(-0.0095, 0.0063)
H - O	(-0.0082, -0.0010)*
N-B - C	(-0.0118, -0.0003)*
N-B - E	(-0.0113, 0.0069)
N-B - O	(-0.0108, 0.0005)
C - E	(-0.0042, 0.0119)
C - O	(-0.0038, 0.0055)
E - O	(-0.0107, 0.0047)

TABLE 8.--DEATH-RATE ESTIMATES BASED ON LEAST 1.25 POWER DEVIATIONS

H	N-B	C	E	O
0.0202	0.0195	0.0255	0.0227	0.0248

5% simultaneous intervals for differences

H - N-B	(-0.0050, 0.0064)
H - C	(-0.0098, -0.0009)*
H - E	(-0.0083, 0.0031)
H - O	(-0.0074, -0.0017)*
N-B - C	(-0.0117, -0.0005)*
N-B - E	(-0.0100, 0.0034)
N-B - O	(-0.0108, 0.0002)
C - E	(-0.0033, 0.0089)
C - O	(-0.0036, 0.0051)
E - O	(-0.0078, 0.0038)

We must note that the effects of combining these robust estimation procedures with jackknifing have not been explicitly studied. The connection of jackknifing with t- and F-tests is particularly close, in that jackknifing is intended to reduce bias in terms of averages and to provide mean squares whose average values are almost correct. For such tests, the greatest difficulty, which is usually not too serious, arises from loss of degrees of freedom and is confined to

situations that are usually easily identifiable. According to our present understanding of jackknifing and robust estimation, we expect the largest part of these good features to continue in the present case, but we must admit that this view rests on understanding and judgment, rather than on trial or theory.

We turn now to a consideration of the 5×5 table of death rates (means of pseudo-values) for anesthetic agents vs. populations, Table 9. We will again look only at analysis VIII.

Corresponding to this is a table of the standard deviations of these numbers (Table 10), as computed from the pseudo-values. (The pseudo-values themselves appear in Appendix 5.)

One instructive table (Table 11) is computed by using the fact that, if $y = \ln x$, then $\sigma_y \approx \frac{\sigma_x}{x}$, and estimating the standard error of the logarithms of the death rates in Table 9. We see that all these standard errors are more-or-less the same, except that those involving either the ether population or ether as an anesthetic are noticeably larger.

If we neglect this, we can pool the standard errors of Table 11 to give a combined mean square of 0.0491 on 825 d.f. (This 825 should not be interpreted literally, inasmuch as the elements in the 5×5 tables are not independent, but we may assume that the correct figure is still very large.) Fitting an additive model to the logarithms of the death rates gives a mean square of 0.2344 on four d.f. for population differences and a mean square of 0.1003 on four d.f. for agent differences. We can therefore form Table 12, the analysis-of-variance-like table. Here, too, we could have omitted ether, getting instead Table 13.

The last two tables must be taken with a grain of salt and not construed as a proper test of significance. But they are instructive in indicating that the kinds of patients given the various anesthetics are distinctive in terms of age, risk, and operation, even after the pooling involved in forming smear-and-sweep categories. We also see again here that, when we are not deceived by the excessive variance of ether, nor too seriously bothered by outliers, we can show clearly that the differences between agents are significant.

It is interesting to look at the estimates of logarithmic main effects. They are (to base e):

	H	N-B	C	E	O
agent	-0.1043	-0.0577	0.1759	-0.1392	0.1253
population	-0.1767	-0.1970	0.2985	-0.0755	0.1507

We have referred several times to analysis VIII. We chose this analysis for two reasons: (1) the choices of the parameters in this analysis are the ones we prefer, as discussed immediately below; and (2) it has the smallest value of the criterion introduced at the end of the last section, as we can see in Table 1. We mention in passing that the values of this criterion are extremely small if we interpret them as interaction sums of squares and compare them with the mean squared error of Table 12. It is better to think of the criterion as the error in an approximation--an approximation that we see is exceedingly good.

TABLE 9.--STANDARDIZED DEATH RATES FOR FIVE AGENTS ON FIVE POPULATIONS
(from analysis VIII)

Population	Agent				
	H	N-B	C	E	O
H	0.0172	0.0169	0.0219	0.0154	0.0205
N-B	0.0164	0.0173	0.0214	0.0148	0.0203
C	0.0261	0.0274	0.0346	0.0267	0.0327
E	0.0178	0.0190	0.0240	0.0182	0.0226
O	0.0221	0.0240	0.0301	0.0219	0.0296

TABLE 10.--STANDARD ERRORS OF ENTRIES IN TABLE 9

Population	Agent				
	H	N-B	C	E	O
H	0.0020	0.0024	0.0026	0.0045	0.0026
N-B	0.0029	0.0022	0.0028	0.0051	0.0031
C	0.0061	0.0043	0.0046	0.0079	0.0056
E	0.0058	0.0054	0.0050	0.0044	0.0061
O	0.0066	0.0037	0.0037	0.0082	0.0045

TABLE 11.--APPROXIMATE STANDARD ERRORS OF LOGARITHMS OF DEATH RATES IN TABLE 9

Population	Agent				
	H	N-B	C	E	O
H	0.114	0.141	0.118	0.295	0.125
N-B	0.178	0.126	0.129	0.348	0.155
C	0.236	0.157	0.132	0.296	0.172
E	0.327	0.285	0.208	0.242	0.269
O	0.300	0.155	0.124	0.374	0.152

FURTHER CONSIDERATION OF THE PARAMETERS

In considering the question of what parameter values are best, the simplest problem is

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TABLE 12.--ANALYSIS OF LOGARITHMS OF DEATH RATES

	Mean square	d.f.	F
Population	0.2344	4	4.78 (very significant)
Agent	0.1003	4	2.05
Error	0.0491	825	

TABLE 13.--ANALYSIS OF LOGARITHMS OF DEATH RATES (OMITTING ETHER)

	Mean square	d.f.	F
Population	0.2404	3	8.9 (very significant)
Agent	0.0760	3	2.8 (significant)
Error	0.0270	528	

that of the choice of M. We may approximate the problem by considering the estimator

$$\frac{D+Mp'}{kR+M},$$

where

D is binomial, mean Np and variance Np(1-p),
R is Poisson, mean N/k and variance N/k,
p′ has mean p and variance σ^2,
D, R, and p′ are independent, and
k is the inverse of the sampling fraction.

Then by the theory of propagation of error we find that to leading order the mean squared error of this estimator as an estimate of p is

$$\frac{Np(1+kp-p) + M^2\sigma^2}{(N+M)^2},$$

which is minimized when $M = \frac{p(1+kp-p)}{\sigma^2}$.

In this study, k may be taken as 25 and we may obtain estimates of σ^2 by looking at the residuals when p′ is obtained by fitting. Because we used a square root transformation, $\sigma^2 \approx 4p \times$ (average squared residual). For the sake of robustness, we have chosen to estimate the average squared residual as the square of the 70th percentile of the squared residuals. For the three permutations of age, risk, and operation we get Table 14. We see that for the average death rate in the Study, 2 percent, M = 500 is a fairly reasonable choice, but for a higher death rate, such as 20 percent, a much larger M, such as 2000, seems better. Because the cells that we are most concerned about are those with few data, which typically are those with high death rates, it seems that M = 5000 might have been a better choice than the 500 we used in most of our analyses.

As a further comment on this, in Table 15 we repeat from Table 1 the values of our criterion for analyses V, VI, and VII, which differ only in the choice of M, and similarly for analyses I and III.

The next question is what transformation one should use to fit for p′. For this we consider analyses IV and V, which differ only in that IV used the logarithmic transformation and V used the square root. The criterion values were 0.0508 and 0.0138, respectively, indicating that the square root was better. But separate evidence may be obtained by reordering the residual tables so that the rows and columns are in order of increasing main effects. For analysis IV, using the logarithm, we get Table 16. For analysis V, using the square root, we get Table 17.

The pattern of minus signs from upper left to lower right in Table 16 is an indication that the curvature in the transformation was too strong. (If it had been too weak, the diagonal would have had a band of plus signs, with minus signs in the upper right and lower left corners, as the less marked pattern in Table 17 tends to show.) These statements can be made more quantitative by counting the excess of plus signs in the indicated corners of Tables 16 and 17, subtracting the resulting excesses in the upper right and lower left from those in the upper left and lower right. Carrying out the calculation gives -52 for Table 16 but +26 for Table 17, indicating that the best transformation is between these two, closer to the square root (perhaps close to the cube root).

TABLE 14.--BEST VALUES OF M ACCORDING TO SIMPLE MODEL

Variables smeared on	Estimated σ^2	Optimal M	
		p = 0.2	p = 0.02
A and R	0.000275 p	21,000	5,400
AR and O	0.00364 p	1,590	406
O and A	0.00110 p	5,250	1,350
OA and R	0.0061 p	950	240
O and R	0.00347 p	1,670	430
OR and A	0.00252 p	2,300	590

TABLE 15.--EFFECT OF M ON THE CRITERION

Analysis	M	Criterion
V	5000	0.0138
VI	500	0.0392
VII	50	0.0365
I	5000	0.0164
III	500	0.0943

TABLE 16.--SIGNS OF RESIDUALS OF FIT TO LN CRUDE OPERATION BY RISK DEATH RATES

-	-	-	-	+	+	+	+
-	+	-	-	+	+	+	+
-	+	-	-	+	+	+	-
-	+	-	-	+	-	+	+
-	-	-	+	+	+	-	+
+	+	-	+	-	+	-	+
+	+	-	+	-	-	-	+
-	-	-	+	-	+	+	+
+	+	-	-	-	+	-	-
-	+	+	-	+	-	+	-
+	-	-	+	-	+	+	+
+	-	+	+	-	+	+	-
-	-	-	+	+	-	+	-
+	+	+	-	-	+	-	+
+	-	-	-	-	+	+	+
+	+	-	-	-	-	+	+
+	+	+	+	+	-	-	+
+	+	-	-	-	+	-	+
+	+	+	-	-	-	-	-
-	-	+	+	-	-	-	-
+	-	+	+	-	-	-	-
+	+	+	-	+	-	+	-
+	+	+	-	+	-	-	-
+	+	+	+	-	-	-	-
-	+	+	+	+	-	+	-

TABLE 17.--SIGNS OF RESIDUALS OF FIT TO SQRT CRUDE OPERATION BY RISK DEATH RATES

-	+	+	+	+	-	+	-
-	+	+	-	+	-	-	-
-	+	+	-	+	-	+	-
+	+	+	+	+	-	-	-
+	+	-	+	-	-	-	+
+	+	-	-	-	-	-	+
+	+	-	-	-	+	-	+
+	+	+	-	+	+	-	-
+	-	-	+	-	+	+	-
-	+	+	-	+	-	+	-
+	-	-	+	-	+	+	+
+	+	+	+	+	-	-	-
-	-	-	-	-	+	-	+
-	+	-	-	+	-	-	+
-	-	-	+	+	-	+	+
-	-	-	-	-	+	+	+
-	-	-	-	-	-	+	+
-	-	+	+	-	-	-	-
-	-	+	-	-	-	-	+
+	+	+	-	+	-	+	-
-	-	+	+	+	+	-	+
-	-	-	-	-	-	+	+
-	-	+	+	-	+	-	+
-	-	+	-	+	+	+	-
-	-	+	+	+	-	+	-

To consider what order the variables should be used in, and the related question of how many variables to use, we could argue by analogy with stepwise regression that the most important variables should be used first, and that in general we should use as few variables as possible, using a variable only if it substantially affects the results. The analogy seems inappropriate to smear-and-sweep, however, because this is an ordering and partition problem, which must be rather more like ordering punchcards, where any preliminary passes on irrelevant variables do not detract from the final results, but final irrelevant passes can be quite harmful. (The serious harmfulness of irrelevant passes in sorting is clearly a false analogy, but mild harmfulness from using an irrelevant variable in the last smear-and-sweep is quite possible.)

If we consider analyses III, VI, and VIII, which differ only in order, and analyses IX, X, XI, and XII, which also differ only in order, we have Table 18. (Because the order of the first two variables is irrelevant, we have given both orders.) Because we have reason to believe that operation is the most important variable, the comparison of the first three looks right. On the other hand, because we believe that length of anesthesia (L) is less important than at least two of the other three variables, we would expect that using it first would be preferable to using it last,

TABLE 18.--EFFECT OF ORDER ON THE CRITERION

Analysis	Variables used	Criterion
III	AOR=OAR	0.0943
VI	ORA=ROA	0.0392
VIII	ARO=RAO	0.0132
IX	ORAL=ROAL	0.0755
X	AORL=OARL	0.0257
XI	LOAR=OLAR	0.0405
XII	LORA=OLRA	0.0249

which these comparisons tend to confirm. Indeed, it might well be that using it first would improve the results, and using it last would degrade them, although we do not have any direct comparisons to check this.

Finally, we come to the sweeping process. Here we have very little to guide us. If we accept our present pickup rule, then how many categories should we use? Presumably, we want to use as many categories as we can before the variance caused by the categories' being too small becomes greater than the bias reduction from separating unequal death rates. But looking at the variance estimates from analyses I and II, which differ only in the number of categories, we see that using only 12 categories in analysis II gave almost exactly the same variance as did the 24 categories in analysis I. Our criterion had values of 0.0164 and 0.0214 for analyses I and II, respectively, and so it also preferred having more categories. It seems that one would not want very many more than 24 categories, for even with this number the estimated exposed in some of the high-death-rate categories is very small, and hence the death-rate estimates in these categories become unstable.

This brings us back to the question of whether the use of equal numbers of deaths was, in fact, a sensible pickup rule. We have very little to go on here; in fact, no other pickup rule was tried with this analysis. By analogy with stratified sampling, perhaps the ideal rule would be one that gave equal values of the square of the population proportion times the variance of the death-rate estimate in the categories. Unfortunately, we do not know how to realize such a pickup. It is clear that any rule that worked on the basis of equal numbers of estimated exposed would be further from this ideal than our current rule is; for example, in the middle-death-rate operations about three-fifths of all estimated exposed correspond to combinations of the variables with death rates below 0.2 percent. Some pickup rule based on counting estimated exposed but producing decreasing numbers in the categories with higher death rates would be interesting to try, but at present we do not know how they should decrease. One simple modification that would improve the current pickup rule would be to pick up as we do to satisfy a requirement that there be a minimum number of deaths, then to pool those categories with fewer than a minimum number of estimated exposed.

SCOPE OF ANALYSIS

In interpreting our results, it is important that we be very clear about the exact question or questions to which they respond. The aspect about which we are most likely to be confused is the extent to which institutional differences have been dealt with. The jackknife is a new technique; accordingly, it is easy to fail to note some of its detailed workings.

What the jackknife has done for us is to allow a proper test of significance, oriented toward the question:

> In a population of institutions from which these 34 are a reasonable sample, what reliable differences are there among death rates that are pooled over institutions but standardized over categories?

What the jackknife has not done for us is to make any allowance for indirect effects springing from differences in institutional death rates over and above those accounted for by standardization over categories. Chapter IV-6 shows that such differences exist. Because we are keenly aware that institutions use different agents with different relative frequencies, the possibility of such indirect effects is well established. Appendix 7 makes exploratory and illustrative calculations of how large these indirect effects might be, and concludes that they are likely to be small and unlikely to alter the conclusions found in this chapter, although there is a bare possibility that they might be shown to do so.

CONCLUSIONS

The most evident conclusion from the results of this analysis is that, for the middle-death-rate operations, there appears to be a significant difference in the standardized death rates associated with the various agents. Halothane and nitrous oxide-barbiturate have lower rates, and cyclopropane and Other have higher ones.

This conclusion appears to be valid, whether we talk about death rates standardized to the over-all population or death rates standardized to the individual populations to which the various anesthetics are customarily applied. Looking at one of these populations seems merely to change all five of the standardized death rates by a multiplicative factor.

Another important conclusion is that, owing to their high variance, very little can be said about the ether death rates. This may be obvious, inasmuch as ether is so infrequently used, but it is well to keep it in mind.

The significant differences between hospitals, commented on elsewhere, are interesting; perhaps more interesting is the apparent long-tailedness of the distribution of death rates, the presence of so many outliers.

Expected, but reassuring, was the significant difference between the populations exposed to the various agents, for it meant that this information had not been lost in the smearing and sweeping.

With respect to what we have learned about smear-and-sweep itself through this study, not very much can be said. The practical details of applying it as a technique have been solved, perhaps, but further theoretical insight into its behavior seems needed. The very consistency of the results, regardless of the choice of the parameters, which increases our confidence in the foregoing conclusions, means that we have difficulty using this analysis to learn the choices of parameters to be preferred. For instance, does this consistency imply that in general the choice of parameters is unimportant, or does it imply that the results with the halothane data were so obvious that the parameter choice had little effect? (One result of this consistency was the decision not to try any other parameter combinations, because it was felt that not enough new would be learned to warrant the additional effort required as a result of the departure of several members of the staff.)

It is perhaps useful to point out that throughout this analysis we have been dealing with quantities only barely detectable above the noise. No study much smaller than the National Halothane Study could have been successful in resolving the observed differences in the death rates as significant.

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APPENDIX 1 TO CHAPTER IV-4

(EQUALLY WEIGHTED) JACKKNIFING IN UNEQUAL-SIZED BLOCKS

Consider an estimator $f(x_1, \ldots, x_N)$ such that

$$E[f(x_1, \ldots, x_N)] = \theta + \frac{\alpha}{N}.$$

We wish to find the expectation of the jackknifed version of this estimator, where we use B blocks, of size $Nk_1, Nk_2, \ldots, Nk_B$; $\sum_i k_i = 1$.

The ith pseudo-value is $B \cdot f(x_1, \ldots, x_N) - (B-1) \cdot [f$ calculated from all data but the ith block$]$. The expectation of the average of the pseudo-values, therefore, is:

$$B \cdot E[f(x_1, \ldots, x_N)] - (B-1) \cdot \operatorname{ave}_i E[f \text{ calculated from all data but the ith block}]$$

$$= B\left(\theta + \frac{\alpha}{N}\right) - \frac{(B-1)}{B} \sum_i \left\{\theta + \frac{\alpha}{N-Nk_i}\right\}$$

$$= \theta + \frac{\alpha}{N} \sum_i \left\{1 - \frac{(B-1)}{B} \frac{1}{1-k_i}\right\}$$

$$= \theta + \frac{\alpha}{NB} \sum_i \left\{\frac{1-Bk_i}{1-k_i}\right\}.$$

If we may assume that all the k_i are small, we can expand the denominator so that the bias is approximately

$$\frac{\alpha}{NB} \sum_i (1-Bk_i)(1+k_i) = \frac{\alpha}{NB} \sum_i \left(k_i - Bk_i^2\right)$$

$$= -\frac{\alpha}{NB} \left(\sum_i Bk_i^2 - 1\right)$$

$$= -\frac{\alpha B}{N} \left(\frac{1}{B} \sum_i (k_i - \bar{k})^2\right)$$

$$= -\frac{\alpha B}{N} \operatorname{var}(k_i),$$

which we may prefer to think of as

$$-\frac{\alpha}{N} \left\{\frac{\operatorname{var}(k_i)}{\operatorname{ave}(k_i)}\right\}.$$

One example we might think of considering is all operations, with hospitals as blocks. In this case B = 34, N = 856,865, and $\operatorname{var}(k_i) = 0.00045723$; hence, jackknifing multiplied the original bias by the factor -0.0156, reducing it by a factor of more than 60.

NOTE: Had we chosen weights in the jackknife, which we did not, we could have made the 1/N bias zero, as occurs with equal-sized blocks.

APPENDIX 2 TO CHAPTER IV-4

STANDARDIZATION IN BROAD GROUPS

The purpose of standardizing the death rates in the smear-and-sweep analysis is to adjust the death rates to correct for the effects of applying the agents to different populations. When we standardize in broad groups, however, such as the categories in the smear-and-sweep analysis, we can correct only for the group-to-group differences; we are unable to correct any imbalances within groups. This leads us to wonder about the magnitudes of such within-group biases. Could the high cyclopropane death rate be due to cyclopropane's being given to worse patients than was halothane, within each category? We can try to estimate the magnitude of such an effect.

Let us assume that there is some variable θ, over which these categories have been defined. In our case this is some composite of age, risk, and operation, for example. The distribution of the true values of θ for patients in category i is $f_i(\theta)$. We wish to compare the agents at the same value of θ, but the only proportions we can observe are for the entire category. Thus, although the proportion of those patients having variable value θ who are given agent a is $\gamma(a,\theta)$, we can observe only the average proportion of category i who receive agent a, $c_i = \int \gamma(a,\theta) f_i(\theta) d\theta$. Similarly, although the proportion of patients having variable value θ and receiving agent a who die is $\delta(a,\theta)$, we can observe only the average proportion who are given a and then die, $\int \delta(a,\theta)\gamma(a,\theta) f_i(\theta) d\theta$, or, normalizing by c_i, the average proportion of those receiving agent a who die,

$$d_i = \frac{\int \delta(a,\theta)\gamma(a,\theta) f_i(\theta) d\theta}{\int \gamma(a,\theta) f_i(\theta) d\theta} .$$

If the imbalances are small, we can study them by expanding γ and δ about μ_i, the mean value of θ in the category, getting

$$\gamma(a,\theta) = \gamma_0(a) + \gamma_1(a)(\theta-\mu_i) + \gamma_2(a)(\theta-\mu_i)^2 + \dots$$

$$\delta(a,\theta) = \delta_0(a) + \delta_1(a)(\theta-\mu_i) + \delta_2(a)(\theta-\mu_i)^2 + \dots .$$

Then, using $\sigma_i^2 = \int (\theta-\mu_i)^2 f_i(\theta) d\theta$, the variance of θ in the category, we find that the proportion in category i exposed to a is approximately

$$c_i = \gamma_0(a) + \gamma_2(a)\sigma_i^2,$$

and that the proportion in category i exposed to a who die is approximately

$$\delta_0(a)\gamma_0(a) + \{\gamma_2(a)\delta_0(a) + \gamma_1(a)\delta_1(a) + \gamma_0(a)\delta_2(a)\}\sigma_i^2.$$

The estimated death rate associated with agent a in category i is thus

$$d_i = \delta_0(a) + \frac{\gamma_1(a)\delta_1(a) + \gamma_0(a)\delta_2(a)}{\gamma_0(a) + \gamma_2(a)\sigma_i^2}\sigma_i^2 .$$

If we regard the final categories of the smear-and-sweep as an approximation to such a variable θ, we can use the data in Appendix 6 to estimate this second term and its cumulative effect. The observed proportion exposed, c, and death rate, d, can be plotted against category number, from which γ_1, γ_2, γ_0, δ_1, and δ_2 can be estimated, and then the observed death rate can be corrected to δ_0. The variances σ_i^2 must, however, be chosen, and we took $\sigma_i^2 = 1$. This choice corresponds to having over 95 percent of the patients in the correct category, or in the one next to it, or in the one next to that.

Carrying out the computations, as on work sheets 1 and 2, we find that the total effect would be that the halothane death rate was estimated 0.000195 too high, and the cyclopropane death rate 0.000420 too high. Moreover, the greatest part of this was the influence of δ_2, the curvature of the death rate across categories. This analysis suggests that in our problem the effect of standardizing in broad groups is negligible.

WORK SHEET 1

ESTIMATING BIAS OF CYCLOPROPANE DEATH RATE

Category	Observed proportion (c)	γ_1	γ_2	γ_0	Observed death rate (d),%	δ_1	δ_2	$\gamma_1\delta_1$	$\gamma_0\delta_2$	Correction term to death rate $\frac{\gamma_1\delta_1+\gamma_0\delta_2}{c}$	δ_0
1	0.1575	0.0002	0.0004	0.157	0.188	0.90	0.000	0.00018	0	0.0011	0.187
2	0.122	0.0010	0.0004	0.122	0.884	0.90	0.000	0.00090	0	0.0074	0.877
3	0.150	0.0020	0.0005	0.149	2.047	0.90	0.000	0.00180	0	0.0120	2.035
4	0.162	0.0030	0.0006	0.161	2.803	0.90	0.013	0.0027	0.0020	0.0271	2.776
5	0.1325	0.0044	0.0006	0.132	3.697	0.95	0.025	0.0042	0.0033	0.057	3.640
6	0.2025	0.0056	0.0006	0.202	3.736	1.00	0.013	0.0056	0.0025	0.040	3.696
7	0.132	0.0070	0.0006	0.131	6.090	1.00	0.013	0.0070	0.0017	0.066	6.024
8	0.168	0.0082	0.0006	0.167	6.760	1.05	0.025	0.0086	0.0042	0.076	6.684
9	0.157	0.0094	0.0006	0.156	8.316	1.10	0.025	0.0103	0.0039	0.090	8.226
10	0.233	0.0105	0.0005	0.232	6.552	1.15	0.025	0.0121	0.0058	0.077	6.475
11	0.134	0.0116	0.0006	0.133	13.233	1.20	0.038	0.0139	0.0051	0.142	13.091
12	0.278	0.0130	0.0006	0.277	7.167	1.30	0.050	0.0169	0.0138	0.110	7.057
13	0.166	0.0141	0.0005	0.165	12.665	1.40	0.075	0.0197	0.0124	0.193	12.472
14	0.156	0.0150	0.0004	0.156	17.860	1.60	0.100	0.0240	0.0156	0.254	17.606
15	0.214	0.0158	0.0002	0.214	13.014	1.80	0.125	0.0284	0.0268	0.258	12.756
16	0.210	0.0158	-0.0002	0.210	13.471	2.10	0.200	0.0332	0.0420	0.358	13.113
17	0.260	0.0150	-0.0006	0.261	16.034	2.60	0.288	0.0390	0.0752	0.440	15.594
18	0.352	0.0132	-0.0010	0.353	17.558	3.25	0.378	0.0429	0.1332	0.502	17.056
19	0.304	0.0110	-0.0011	0.305	22.006	4.10	0.438	0.0451	0.1336	0.588	21.418
20	0.296	0.0088	-0.0011	0.297	27.315	5.00	0.513	0.0440	0.1523	0.663	26.652
21	0.326	0.0065	-0.0011	0.327	29.844	6.15	0.600	0.0400	0.1960	0.724	29.120
22	0.188	0.0044	-0.0009	0.189	38.727	7.40	0.688	0.0326	0.1300	0.865	37.862
23	0.340	0.0030	-0.0006	0.341	37.836	8.90	0.788	0.0267	0.2685	0.869	36.967
24	0.341	0.0018	-0.0006	0.342	58.855	10.50	0.978	0.0189	0.334	1.035	57.820
25	0.540	0.0007	-0.0004	0.540	70.385	12.80	1.088	0.0090	0.588	1.105	69.280

WORK SHEET 2

ESTIMATING BIAS OF HALOTHANE DEATH RATE

Category	Observed proportion (c)	γ_1	γ_2	γ_0	Observed death rate (d),%	δ_1	δ_2	$\gamma_1\delta_1$	$\gamma_0\delta_2$	Correction to death rate $\frac{\gamma_1\delta_1+\gamma_0\delta_2}{c}$	δ_0
1	0.352	-0.0002	-0.00026	0.352	0.134	0.60	0.00	-0.00012	0	-0.0003	0.134
2	0.356	-0.0007	-0.00026	0.356	0.685	0.60	0.00	-0.00042	0	-0.0012	0.687
3	0.331	-0.0012	-0.00026	0.331	1.498	0.60	0.025	-0.00072	0.0083	0.0230	1.475
4	0.329	-0.0018	-0.00026	0.329	2.394	0.65	0.025	-0.00117	0.0082	0.0213	2.373
5	0.372	-0.0023	-0.00026	0.372	2.284	0.70	0.025	-0.00161	0.0093	0.021	2.263
6	0.296	-0.0028	-0.00026	0.296	2.518	0.75	0.025	-0.0021	0.0074	0.018	2.500
7	0.320	-0.0033	-0.00026	0.320	3.975	0.80	0.025	-0.0026	0.0080	0.017	3.958
8	0.312	-0.0038	-0.00026	0.312	5.339	0.85	0.025	-0.0032	0.0078	0.015	5.324
9	0.334	-0.0044	-0.00026	0.334	6.023	0.90	0.025	-0.0040	0.0084	0.013	6.010
10	0.306	-0.0049	-0.00026	0.306	6.454	0.95	0.025	-0.00455	0.00765	0.010	6.444
11	0.362	-0.0054	-0.00026	0.362	5.490	1.00	0.038	-0.0054	0.0138	0.023	5.467
12	0.254	-0.0059	-0.00026	0.254	9.443	1.10	0.050	-0.0065	0.0127	0.024	9.419
13	0.316	-0.0064	-0.00026	0.316	8.401	1.20	0.075	-0.0077	0.0246	0.054	8.347
14	0.349	-0.0070	-0.00026	0.349	10.165	1.35	0.075	-0.0094	0.0262	0.048	10.127
15	0.302	-0.0075	-0.00026	0.302	11.310	1.50	0.088	-0.0112	0.0268	0.052	11.258
16	0.215	-0.0080	-0.00026	0.215	24.749	1.70	0.125	-0.0136	0.0269	0.062	24.687
17	0.268	-0.0085	-0.00026	0.268	16.303	2.00	0.150	-0.0170	0.0402	0.086	16.217
18	0.237	-0.0090	-0.00026	0.237	17.546	2.30	0.212	-0.0207	0.0503	0.125	17.421
19	0.251	-0.0096	-0.00026	0.251	16.124	2.85	0.362	-0.0273	0.0909	0.253	15.871
20	0.298	-0.0101	-0.00026	0.298	22.168	3.75	0.512	-0.0378	0.1525	0.384	21.784
21	0.204	-0.0106	-0.00026	0.204	27.963	4.90	0.912	-0.0520	0.1860	0.657	27.306
22	0.279	-0.0111	-0.00026	0.279	23.157	7.40	1.35	-0.082	0.377	1.057	22.100
23	0.189	-0.0116	-0.00026	0.189	39.200	9.30	2.00	-0.108	0.378	1.428	37.872
24	0.263	-0.0122	-0.00026	0.263	31.665	11.40	1.00	-0.139	0.263	0.472	31.193
25	0.039	-0.0127	-0.00026	0.039	100.000	13.00	1.00	-0.165	0.039	-3.23	100.00

APPENDIX 3 TO CHAPTER IV-4

ESTIMATION BIAS IN SMEAR-AND-SWEEP

The basic step in smear-and-sweep is the construction of a relatively effective, simple classification based on several background variables while consciously and completely neglecting the variable under study. From the point of view of estimation of the effect of the variable under study, this procedure tends to make differences found smaller than differences present (i.e., nearer to zero, but of the same sign).

The reason for this reduction is easily seen in an unrealistically extreme example. Suppose that only two anesthetics are being studied, that they have quite different death rates, and that only one of them is used in each combination of operation nd age. Here the OA smear-and-sweep, which we may suppose to be the first step in the procedure, will sweep cases treated with one anesthetic almost entirely into low-death-rate categories and the other almost entirely into high-death-rate categories. Comparison within categories, whether individual or based on standardized death rates, will now show only a trace of the true difference between anesthetics.

Let us consider a purely hypothetical example in which this effect is present to a substantial but not extreme degree. Suppose, first, that agent B is always twice as dangerous as agent A, while eight age-operation cells (all high-risk) have risks differing by rather smaller ratios and the two agents are preferentially used, as indicated in Table 1.

If these death rates were to apply exactly, without sampling fluctuation, the observed death rates per 1000 by cell (without subdivision by agent) would be as shown in Table 2, so that, if two categories are to be formed from the eight cells, the asterisked cells will be combined into the higher-risk category (the other four forming the lower-risk category).

If 1000 administrations were to occur in each of the eight cells, and the observed numbers of deaths happened to match exactly the average numbers corresponding to the assumed death rates, the results by category would appear as shown in Table 3.

As a result, the mean ratio of death rates would be 1.58, notably reduced from the ratio of 2.00, which, according to the assumptions of this hypothetical example, actually applies in every cell.

In more realistic situations, we may expect much weaker effects of the same kind. In the present study, where imbalances in the use of anesthetics are much less extreme, judgment suggests a pulling together of estimated death rates by a few hundredths of the true differences, which is surely not important.

Rather than trying to obtain bounds for such an effect, the reasonable approach in studies in which such an effect is a matter of concern is to redo the analysis in such a way as to remove the effect, at least in large part. Although the effect is not here a matter of concern, a brief description of how such a computation might proceed in the National Halothane Study may be helpful in other studies.

Two approaches for the near elimination of the effect of imbalance are possible:

Approach 1: Calculate the death rate for each cell of the smear to be used in the pickup rule for determining the sweep as follows:

- (1a) Fix a single set of weights for the agents.
- (1b) Calculate separate estimated death rates by agent for each cell.
- (1c) Form weighted mean death rates, to be used in the pickup rule, from these estimates, using the same single set of agent weights for all cells.

Approach 2: Calculate an adjusted death rate for each cell as follows:

- (2a) Use a preliminary analysis to estimate over-all death rates (i.e., for all cells combined) by agent (which will be applied within individual cells as if appropriate there).
- (2b) Adjust the estimated numbers exposed in each cell to equivalent numbers exposed to a standard agent, using the relative over-all death rates from (2a).
- (2c) Use these equivalent estimated exposed, in combination with observed deaths, to form the death rates used in the pickup rule.
- (2d) Iterate steps (2a), (2b), and (2c) if the relative over-all death rates change appreciably.

Why does approach 1 work? By being wasteful, we could avoid bias of pickup (due to differing distributions by agent within cells) by winnowing to get balance, discarding cases (randomly selected within agent) until the proportions by agent are the same in each cell. When we have done this, the cell death rate for the winnowed cells will be the sum of the agent-by-cell death rates weighted by these fixed proportions. Approach 1 replaces these agent-by-cell death rates based on winnowed samples with corresponding rates based on all available cases, and

TABLE 1.--DISTRIBUTION OF CASES AND DEATH RATES IN THE EIGHT AGE-OPERATION CELLS FOR THE EXAMPLE

Age/operation	True agent death rates %		Cases by agent %	
	X	Y	X	Y
20-49	11A, 22B	16A, 32B	10A, 90B	70A, 30B
50-59	12A, 24B	17A, 34B	30A, 70B	90A, 10B
60-69	13A, 26B	18A, 36B	50A, 50B	100A
70-	15A, 30B	20A, 40B	70A, 30B	100A

TABLE 2.--OBSERVED DEATH RATES PER 1000 FOR THE EXAMPLE

Age/operation	X	Y
20-49	209*	208*
50-59	204*	187
60-69	195	180
70-	195	200*

TABLE 3.--OUTCOME OF EXAMPLE WHEN GROUPED BY DEGREE OF RISK

Higher-risk category

Operation	Age	A's exposed	A's dead	B's exposed	B's dead
X	20-49	100	11	900	198
X	50-59	300	36	700	168
Y	20-49	700	112	300	96
Y	70-	900	180	100	40
Total		2000	339	2000	502
Death rate			17.0%		25.1%
Ratio of death rates = 1.48					

Lower-risk category

Operation	Age	A's exposed	A's dead	B's exposed	B's dead
X	60-69	500	65	500	130
X	70-	700	105	300	90
Y	50-59	1000	170	none	none
Y	60-69	1000	180	none	none
Total		3200	520	800	220
Death rate			16.2%		27.5%
Ratio of death rates = 1.69					

is equally resistant to all forms of bias due to unbalanced use of agents within cells.

It is, of course, nice to use approach 1 whenever one can, because it does not use strong assumptions. To use it we require reasonable amounts of data from each agent in each smear cell. In the halothane situation this requirement seems likely to be too stringent.

Approach 2, which can be used with far fewer data, is based on a more restrictive assumption, namely, that agent-by-cell death rates can be satisfactorily taken as products of an agent factor and a cell factor. Under these circumstances, the agent factors can be taken (iteratively) as proportional to the over-all agent-by-agent results of a previous analysis, and can be applied, by altering, for the smear-and-sweep pickup stages only, the numbers of estimated exposed to equivalent numbers of estimated exposed.

If we wished to improve our estimates in the present study, it would be natural to adopt approach 2. Here the natural choices would seem to be:

(1) set all ether cases aside during smear-and-sweep,
(2) treat halothane and nitrous oxide-barbiturate as equivalent,
(3) treat cyclopropane and Other as equivalent, and
(4) treat the latter as producing about 5/4 the death rate of the former.

These decisions can be implemented, in the notation used above, by:

(1) eliminating all ether deaths from D,
(2) eliminating all ether exposures from EE and calculating an equivalent EE from*

$$\text{equiv EE} = \frac{10}{9}\,(\text{estimated exposed to cyclopropane or Other}) + \frac{8}{9}\,(\text{estimated exposed to halothane or nitrous oxide-barbiturate}),$$

and
(3) carrying out the entire calculation as before.

If the estimated death rates are changed in a substantial way, altering the 5/4 ratio noticeably, a further iteration would be called for.

*The numbers $\frac{10}{9}$ and $\frac{8}{9}$ need to be in the assumed ratio of 5 to 4. The values suggested have the added virtue of producing an equivalent EE close to the unadjusted EE (also with ether cases omitted).

APPENDIX 4 TO CHAPTER IV-4

PSEUDO-VALUES OF OVER-ALL DEATH RATE BY AGENT

(From analysis VIII)

Institution	Agent				
	H	N-B	C	E	O
1	0.021532	0.011965	0.028392	0.025808	0.025037
2	0.027236	0.019895	0.021463	0.027521	0.026733
3	0.022129	0.013047	0.023398	0.023658	0.026837
4	0.010629	0.015829	0.019115	0.020435	0.015473
5	0.034197	0.058306	0.038189	0.022394	0.034358
6	0.013869	0.018885	0.024388	0.019380	0.015489
7	0.026538	0.025576	0.017467	0.045790	0.043684
8	-0.062582	0.029812	0.026021	-0.005365	-0.008451
9	0.033034	0.030567	0.019238	-0.087503	0.012409
10	0.028128	0.021329	0.045466	0.041052	0.033164
11	0.011825	0.024606	0.007382	-0.070818	0.020790
12	0.028894	0.018269	0.026418	0.025706	0.033941
13	0.025234	0.022877	0.047625	0.021613	0.028055
14	0.018598	0.021994	0.018027	0.023803	0.015777
15	0.026865	0.016277	0.022735	0.003114	0.027657
16	0.023574	0.001588	0.025405	0.027627	0.028795
17	0.019178	0.022324	0.022966	0.000938	0.022143
18	0.016668	0.018239	0.012821	0.008850	0.024626
19	0.031989	0.009613	0.034783	0.025210	0.033696
20	0.024192	0.013915	0.018139	0.063541	0.020941
21	0.023809	0.012258	0.009164	0.038633	-0.001531
22	0.023425	0.032466	0.019681	0.027288	0.041386
23	0.018175	0.020125	0.022730	0.023725	0.024531
24	0.027003	0.011354	0.043400	0.044703	0.037946
25	0.024010	0.024885	0.032217	0.034557	0.045610
26	0.021036	0.010147	0.036192	0.026593	0.022822
27	0.016733	0.023318	0.017219	0.025333	0.022545
28	0.020854	0.022067	0.025623	0.025880	0.024496
29	0.018345	0.023480	0.025447	0.023532	0.020832
30	0.018108	0.018971	0.026594	0.023725	0.022686
31	0.024152	0.024683	0.027649	0.024366	0.028690
32	0.013649	0.021564	0.027465	0.023568	0.024410
33	0.000899	-0.005100	0.012118	0.000600	-0.001623
34	0.021096	0.022878	0.037142	0.010878	0.025825

APPENDIX 5 TO CHAPTER IV-4

PSEUDO-VALUES OF STANDARDIZED DEATH RATES FOR ALL FIVE AGENTS WITH ALL FIVE POPULATIONS ON MIDDLE-DEATH-RATE OPERATIONS

(From analysis VIII)

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 1					
H	0.006212	-0.004051	0.010313	0.000677	0.008590
N-B	0.000530	-0.011564	0.000379	-0.004111	-0.000877
C	0.028049	0.019531	0.037071	0.039126	0.032281
E	0.015335	0.009000	0.024672	0.016521	0.023890
O	0.024195	0.011165	0.029029	0.036293	0.021949
PSEUDO-VALUES FOR INSTITUTION 2					
H	0.043230	0.041478	0.039770	0.049101	0.044291
N-B	0.044528	0.034175	0.037453	0.041904	0.042935
C	0.086529	0.064842	0.083562	0.097391	0.093941
E	0.027462	0.020579	0.030048	0.026975	0.035106
O	0.050336	0.039299	0.047762	0.062543	0.054300
PSEUDO-VALUES FOR INSTITUTION 3					
H	0.016027	0.008877	0.018023	0.019107	0.020268
N-B	-0.001355	-0.005483	-0.007818	-0.003188	-0.002248
C	0.030497	0.012619	0.032396	0.038507	0.036213
E	0.021126	0.011640	0.024424	0.018034	0.026192
O	0.012796	0.001209	0.010203	0.012202	0.015774
PSEUDO-VALUES FOR INSTITUTION 4					
H	0.003424	0.001230	0.005305	0.004611	0.002819
N-B	0.013690	0.022417	0.030502	0.018003	0.026450
C	0.054505	0.061246	0.072565	0.070956	0.061397
E	0.027975	0.040248	0.037124	0.040818	0.030573
O	0.052725	0.056824	0.063395	0.069185	0.064219
PSEUDO-VALUES FOR INSTITUTION 5					
H	0.044735	0.062913	0.045792	0.038282	0.045135
N-B	0.038319	0.058937	0.042088	0.034271	0.046411
C	-0.003421	0.030478	0.005591	-0.020656	-0.019559
E	0.034696	0.063248	0.038318	0.038673	0.035675
O	0.051975	0.094979	0.068201	0.051132	0.058982

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 6					
H	0.010684	0.012091	0.016541	0.022915	0.008509
N-B	0.005387	0.010000	0.013929	0.020485	0.004057
C	0.022811	0.026197	0.034132	0.019273	0.027529
E	0.025222	0.036544	0.031426	0.032750	0.021035
O	-0.011442	-0.007794	-0.002228	-0.034856	-0.009808
PSEUDO-VALUES FOR INSTITUTION 7					
H	0.027889	0.025702	0.022126	0.045306	0.041627
N-B	0.022754	0.022583	0.016806	0.038607	0.036592
C	0.053576	0.044800	0.038158	0.079202	0.082198
E	0.038516	0.031858	0.026772	0.043449	0.054932
O	0.042341	0.044908	0.029962	0.072296	0.063527
PSEUDO-VALUES FOR INSTITUTION 8					
H	-0.007255	0.031351	0.047649	0.029725	0.006339
N-B	-0.053767	0.004585	0.002159	-0.008684	-0.029360
C	-0.122940	0.051241	0.036970	0.009528	0.004899
E	-0.147924	-0.103404	-0.094693	-0.097941	-0.143637
O	-0.177590	-0.021082	-0.034305	-0.140306	-0.061509
PSEUDO-VALUES FOR INSTITUTION 9					
H	0.025287	0.023053	0.016168	-0.088070	0.008199
N-B	0.012987	0.008918	0.003148	-0.084866	-0.008783
C	0.053372	0.052248	0.031687	-0.114412	0.037874
E	0.068877	0.097425	0.079991	-0.000169	0.069747
O	0.047147	0.044936	0.031390	-0.089932	0.021766
PSEUDO-VALUES FOR INSTITUTION 10					
H	0.022189	0.013852	0.041952	0.040505	0.027734
N-B	0.033876	0.031817	0.053355	0.045908	0.042639
C	0.067091	0.052409	0.080505	0.104087	0.065628
E	0.029260	0.025914	0.049175	0.028841	0.031999
O	0.038791	0.036026	0.056126	0.054024	0.047643
PSEUDO-VALUES FOR INSTITUTION 11					
H	0.008604	0.019670	0.007658	-0.053831	0.018957
N-B	0.003993	0.014977	0.001717	-0.080737	0.008874
C	0.036700	0.060288	0.031412	-0.105100	0.046910
E	0.054372	0.075574	0.060693	0.037868	0.075203
O	0.031550	0.040416	0.022814	-0.070181	0.044303

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 12					
H	0.020728	0.013451	0.020199	0.021456	0.027878
N-B	0.021509	0.013609	0.017821	0.019716	0.025647
C	0.023399	0.006693	0.019766	0.011151	0.022407
E	0.026154	0.018993	0.021366	0.018771	0.033576
O	0.043097	0.025481	0.045261	0.040533	0.046492
PSEUDO-VALUES FOR INSTITUTION 13					
H	0.018686	0.015971	0.039761	0.014100	0.020629
N-B	0.020456	0.017498	0.041916	0.016626	0.022786
C	0.025907	0.023481	0.046819	0.022433	0.028758
E	0.024503	0.022148	0.048470	0.018653	0.027551
O	0.022269	0.020322	0.046071	0.015709	0.024904
PSEUDO-VALUES FOR INSTITUTION 14					
H	0.010540	0.013392	0.008240	0.012812	0.007654
N-B	0.006870	0.008855	0.003204	0.009729	0.001451
C	-0.001634	0.002247	-0.002715	-0.000554	-0.005622
E	0.018542	0.023129	0.020710	0.019774	0.016840
O	0.009552	0.014086	0.009129	0.012491	0.007876
PSUEDO-VALUES FOR INSTITUTION 15					
H	0.019382	0.011544	0.015699	0.004814	0.018897
N-B	0.021056	0.014363	0.016096	-0.002178	0.017645
C	0.020626	0.002955	0.017167	-0.015860	0.021708
E	0.054652	0.033925	0.043755	0.033498	0.050320
O	0.040593	0.022692	0.039923	0.036468	0.047369
PSEUDO-VALUES FOR INSTITUTION 16					
H	0.020663	0.012806	0.022414	0.023173	0.025236
N-B	0.033265	0.036308	0.034261	0.031583	0.037408
C	0.040245	-0.012239	0.046230	0.047529	0.050399
E	0.022486	-0.012628	0.021366	0.019805	0.024769
O	0.024900	-0.009518	0.026383	0.032192	0.031747
PSEUDO-VALUES FOR INSTITUTION 17					
H	0.016144	0.018003	0.020284	-0.004261	0.016534
N-B	0.010861	0.010958	0.012615	-0.009544	0.011836
C	0.036285	0.038701	0.033682	0.014454	0.042309
E	-0.039223	-0.038131	-0.047883	-0.042730	-0.044098
O	-0.004652	0.002397	-0.002837	-0.031147	-0.001578

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 18					
H	0.019750	0.023945	0.019586	0.017484	0.028107
N-B	0.018456	0.021123	0.015111	0.013639	0.024708
C	0.047742	0.048006	0.049766	0.041772	0.060611
E	0.013051	0.013376	0.008903	0.007312	0.021364
O	0.028506	0.027621	0.021964	0.018006	0.037502
PSEUDO-VALUES FOR INSTITUTION 19					
H	0.022403	-0.000190	0.025188	0.016738	0.023347
N-B	0.025578	0.006384	0.034534	0.020336	0.030851
C	0.042336	0.020732	0.047377	0.035545	0.048270
E	0.032523	0.006550	0.029206	0.019449	0.030697
O	0.033513	0.009706	0.037533	0.025279	0.035841
PSEUDO-VALUES FOR INSTITUTION 20					
H	0.017879	0.009238	0.010423	0.047164	0.017988
N-B	0.024222	0.015270	0.018549	0.052100	0.027104
C	-0.045153	-0.056012	-0.051805	0.017674	-0.068155
E	0.017212	0.016887	0.011813	0.025841	0.015627
O	0.028056	0.021133	0.022042	0.084773	0.027955
PSEUDO-VALUES FOR INSTITUTION 21					
H	-0.000067	-0.009809	-0.019050	0.005061	-0.021970
N-B	0.021812	0.009240	0.009246	0.029447	-0.001055
C	0.020657	0.015259	0.001806	0.036106	-0.025623
E	0.013342	0.014674	-0.004113	0.022186	-0.006411
O	0.030853	0.011781	0.013191	0.057844	-0.003094
PSEUDO-VALUES FOR INSTITUTION 22					
H	0.019316	0.025528	0.017579	0.021412	0.036124
N-B	0.016101	0.024034	0.016529	0.024625	0.036208
C	0.026976	0.036886	0.017515	0.033309	0.042270
E	0.021284	0.028800	0.017773	0.016748	0.039063
O	0.020506	0.032306	0.015995	0.029994	0.041552
PSEUDO-VALUES FOR INSTITUTION 23					
H	0.014735	0.016105	0.018837	0.019546	0.020544
N-B	0.014467	0.014752	0.018575	0.019275	0.019921
C	0.018856	0.025593	0.024647	0.028405	0.025464
E	0.017478	0.019473	0.021362	0.018894	0.025213
O	0.021292	0.024308	0.027309	0.032232	0.028756

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 24					
H	0.029415	0.019877	0.048139	0.044287	0.042582
N-B	0.044751	0.037993	0.063068	0.064979	0.056128
C	0.061214	0.041107	0.080438	0.083088	0.076309
E	0.024122	0.008500	0.043611	0.032214	0.038080
O	0.045120	0.021240	0.065255	0.071823	0.054433
PSEUDO-VALUES FOR INSTITUTION 25					
H	0.031205	0.028167	0.036743	0.033389	0.047418
N-B	0.025621	0.026836	0.034906	0.035534	0.048702
C	0.059174	0.059478	0.069852	0.087628	0.085506
E	0.024682	0.027252	0.035091	0.031862	0.045966
O	0.057492	0.059131	0.066393	0.075231	0.087060
PSEUDO-VALUES FOR INSTITUTION 26					
H	-0.004866	-0.011323	0.003383	-0.003510	-0.005050
N-B	0.030586	0.014955	0.039998	0.035928	0.033562
C	0.024196	0.006134	0.044486	0.030006	0.020531
E	0.017257	0.004957	0.029656	0.018081	0.018571
O	0.018816	0.010267	0.035948	0.027661	0.021672
PSEUDO-VALUES FOR INSTITUTION 27					
H	0.001336	0.005769	-0.003103	0.007892	0.003100
N-B	0.007045	0.011590	0.004184	0.016332	0.011009
C	0.013860	0.025778	0.017961	0.033002	0.019149
E	0.014180	0.019604	0.018983	0.015861	0.015864
O	0.012643	0.024034	0.010497	0.020918	0.018713
PSEUDO-VALUES FOR INSTITUTION 28					
H	0.013465	0.014728	0.017789	0.017098	0.016878
N-B	0.011016	0.011239	0.014085	0.013641	0.013583
C	0.030920	0.032509	0.034747	0.041120	0.033618
E	0.016592	0.017405	0.020081	0.016129	0.020577
O	0.026677	0.028650	0.032346	0.035400	0.030118
PSEUDO-VALUES FOR INSTITUTION 29					
H	0.018486	0.023237	0.026176	0.023131	0.021405
N-B	0.016648	0.018826	0.022306	0.020339	0.017983
C	0.030197	0.038682	0.039346	0.041425	0.036025
E	0.018065	0.023587	0.024831	0.018591	0.020463
O	0.025689	0.033012	0.036304	0.035409	0.029434

	Agent				
	H	N-B	C	E	O
PSEUDO-VALUES FOR INSTITUTION 30					
H	0.023366	0.025350	0.033474	0.028548	0.029129
N-B	0.019331	0.020718	0.030819	0.025206	0.025721
C	0.027784	0.029075	0.037574	0.035937	0.034923
E	0.016106	0.019331	0.025726	0.018894	0.021463
O	0.024809	0.022857	0.033947	0.031972	0.029806
PSEUDO-VALUES FOR INSTITUTION 31					
H	0.015527	0.016053	0.017268	0.015082	0.019526
N-B	0.016706	0.016142	0.019519	0.017427	0.021500
C	0.024215	0.024819	0.031241	0.022107	0.027327
E	0.022369	0.024630	0.024034	0.018668	0.027687
O	0.028621	0.028793	0.032195	0.029404	0.031892
PSEUDO-VALUES FOR INSTITUTION 32					
H	0.013681	0.021248	0.024948	0.021463	0.021242
N-B	0.008301	0.013518	0.021307	0.015668	0.016233
C	0.019691	0.037472	0.035863	0.034127	0.037158
E	0.011248	0.019435	0.024126	0.016879	0.022727
O	0.012685	0.023412	0.026706	0.026712	0.023764
PSEUDO-VALUES FOR INSTITUTION 33					
H	0.025856	0.028276	0.041161	0.023115	0.029052
N-B	0.003361	0.014865	0.013144	0.012024	0.004225
C	0.044377	0.019782	0.049858	0.035136	0.040570
E	0.004084	0.003639	0.033949	0.049658	0.018457
O	0.032414	0.019905	0.044963	0.029576	0.026907
PSEUDO-VALUES FOR INSTITUTION 34					
H	0.015088	0.016526	0.029600	0.004563	0.019141
N-B	0.017142	0.017613	0.030600	0.003512	0.019503
C	-0.012145	-0.011357	0.001830	-0.025872	-0.010890
E	0.018950	0.020456	0.035261	0.018879	0.022836
O	0.006803	0.001335	0.013053	-0.017912	0.005043

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APPENDIX 6 TO CHAPTER IV-4

MIDDLE-DEATH-RATE OPERATIONS: DEATHS, ESTIMATED EXPOSED, AND DEATH RATES BY AGENT FOR FINAL CATEGORIES

(From analysis VIII)

D: Deaths
E: Estimated exposed
R: Death rate

Final category	Agent					Total
	H	N-B	C	E	O	
1 D	116	80	73	34	70	373
1 E	86661	60576	38839	24305	35821	246204
1 R	0.00134	0.00132	0.00188	0.00140	0.00195	0.00152
2 D	123	88	54	26	91	382
2 E	17947	11831	6111	5695	8884	50470
2 R	0.00685	0.00744	0.00884	0.00456	0.01024	0.00757
3 D	120	77	74	27	76	374
3 E	8011	5765	3614	3151	3639	24182
3 R	0.01498	0.01336	0.02047	0.00857	0.02088	0.01547
4 D	125	72	71	30	74	372
4 E	5221	3803	2532	1568	2692	15818
4 R	0.02394	0.01893	0.02803	0.01913	0.02748	0.02352
5 D	128	81	75	27	70	381
5 E	5604	3504	2028	1410	2479	15026
5 R	0.02284	0.02312	0.03697	0.01914	0.02823	0.02536
6 D	89	81	85	47	71	373
6 E	3534	2452	2275	1529	2119	11910
6 R	0.02518	0.03303	0.03736	0.03072	0.03350	0.03132
7 D	108	81	68	38	79	374
7 E	2716	2108	1116	1097	1447	8485
7 R	0.03975	0.03842	0.06090	0.03464	0.05459	0.04407
8 D	113	73	77	40	79	382
8 E	2116	1587	1139	853	1080	6777
8 R	0.05339	0.04597	0.06760	0.04687	0.07310	0.05636
9 D	131	79	85	53	82	430
9 E	2175	1101	1022	983	1221	6503
9 R	0.06023	0.07173	0.08316	0.05390	0.06715	0.06612

Final category	Agent					Total
	H	N-B	C	E	O	
10 D	109	68	84	27	90	378
10 E	1688	1154	1282	391	1000	5516
10 R	0.06454	0.05891	0.06552	0.06892	0.08999	0.06852
11 D	104	94	93	23	69	383
11 E	1894	1470	702	523	647	5239
11 R	0.05490	0.06391	0.13233	0.04391	0.10653	0.07310
12 D	96	83	80	41	85	385
12 E	1016	841	1116	172	858	4006
12 R	0.09443	0.09859	0.07167	0.23734	0.09899	0.09610
13 D	110	58	87	38	105	398
13 E	1309	655	686	645	838	4135
13 R	0.08401	0.08849	0.12665	0.05890	0.12522	0.09624
14 D	111	81	87	40	77	396
14 E	1091	817	487	122	615	3133
14 R	0.10165	0.09914	0.17860	0.32763	0.12517	0.12638
15 D	106	73	86	40	65	370
15 E	937	447	660	489	564	3099
15 R	0.11310	0.16319	0.13014	0.08178	0.11509	0.11938
16 D	136	94	72	19	74	395
16 E	549	678	534	234	548	2544
16 R	0.24749	0.13861	0.13471	0.08112	0.13499	0.15523
17 D	109	87	104	36	73	409
17 E	668	579	648	98	496	2492
17 R	0.16303	0.15014	0.16034	0.36406	0.14689	0.16409
18 D	89	59	132	32	76	388
18 E	507	295	751	243	341	2138
18 R	0.17546	0.19998	0.17558	0.13145	0.22278	0.18142
19 D	78	76	128	31	76	389
19 E	483	367	581	114	375	1922
19 R	0.16124	0.20684	0.22006	0.27034	0.20247	0.20230
20 D	102	61	123	30	72	388
20 E	460	227	450	166	235	1540
20 R	0.22168	0.26782	0.27315	0.18007	0.30554	0.25188

Final category	Agent					Total
	H	N-B	C	E	O	
21 D	81	53	138	39	95	406
21 E	289	96	462	218	348	1415
21 R	0.27963	0.54936	0.29844	0.17861	0.27228	0.28676
22 D	86	46	97	32	110	371
22 E	371	192	250	98	414	1327
22 R	0.23157	0.23858	0.38727	0.32593	0.26523	0.27946
23 D	73	44	123	37	104	381
23 E	186	117	325	61	295	984
23 R	0.39200	0.37539	0.37836	0.60563	0.35210	0.38681
24 D	64	36	154	22	105	381
24 E	202	83	261	27	193	767
24 R	0.31665	0.43334	0.58855	0.80209	0.54321	0.49637
25 D	52	28	147	27	102	356
25 E	15	68	208	44	49	387
25 R	1.00000	0.40740	0.70385	0.60067	1.00000	0.91878

APPENDIX 7 TO CHAPTER IV-4

APPROXIMATE INQUIRY INTO PLAUSIBLE INDIRECT EFFECT OF DIFFERENCES IN STANDARDIZED DEATH RATES BETWEEN INSTITUTIONS

The existence of differences in standardized death rates from institution to institution is made clear in Chapter IV-6. The purpose of this appendix is to explore the mechanism, and crudely assess the magnitudes, of the indirect effects of such differences on the results of Chapter IV-4. Before discussing the limited calculations that were actually feasible for this purpose, it will be advantageous to discuss what computations might have been made if we had been in a position to start this chapter's computations from the beginning with the intent of compensating for differences in

SMR = actual deaths/standard deaths

from institution to institution.

One approach would have been to arrange the institutions in groups of three or four, stratifying on the basis of SMR values, and then to bring in these institutional groups in a further stage of smear-and-sweep. The result would be a set of categories that involved institutional groups. It would then be quite feasible to estimate death rates by agent standardized on these categories, although the estimation of a standard error for this estimate would be a little complicated, inasmuch as it would have to be based on institutions within institutional groups (and hence within categories). Such an approach is likely to have proved illuminating, had it been feasible. It has the advantage of making no assumption about the ways in which institutional differences combine with differences from operation to operation, or those from age to age, etc. It has the disadvantage of exposure to inadequate control from the allotment of too few categories for the over-all variation that requires control.

At the opposite extreme stand computations based on a very specific rule of combination between the institutional effects and other effects. To understand the essentials of such calculations, we need to consider what would happen if the variation of death rate for institutions did, or did not, arise only because of the differing distributions of patients over the various categories.

(1) If the variation is only according to the distribution over categories:

(1a) The number of standard deaths will equal the number of actual deaths, so that SMR = 100.

(1b) Institution will have no effect on death rate within category, so that no indirect effect of institution can be transmitted into the smear-and-sweep estimates of mortality rates by agent.

(2) If this variation is not only according to the distribution over categories, the death rate in an institution for a category may be (but need not be) representable as a product of an institution factor and a category factor. If this is the case:

(2a) The natural estimate of the institution factor would then be the ratio of actual deaths to standardized deaths, where the standardization is carried out for approximately the factors that enter into the smear-and-sweep estimate.

(2b) Instead of accumulating estimated exposed, EE, by institution, category, and agent (to obtain estimated exposed by category and agent, used as a basis for calculating death rates by category and agent), one should accumulate equivalent estimated exposed, EEE, by institution, category, and agent, thus forming equivalent estimated exposed by category and agent, to serve as denominators for equivalent death rates by agent and category. Here:

$$\text{EEE} = \text{equivalent estimated exposed}$$

$$= \frac{\text{actual deaths}}{\text{standard deaths}} \cdot (\text{estimated exposed})$$

$$= (\text{SMR}) \cdot (\text{EE}).$$

Further procedures, including application of equivalent death rates to suitable populations, jackknifing, and robust estimation, could then proceed just as in the actual analysis.

Regrettably, it did not prove feasible to carry out this computation, either. Although subject to reservations about the adequacy of the assumed multiplicative effect of institution, such computations, especially if used to assess the shift in final comparisons associated with a change from estimated exposed to equivalent estimated exposed, would have high plausibility and serve as strong evidence.

It has been feasible to carry out a very oversimplified analogue of this latter computation, one that involves the estimated distribution of exposure by institution and agent (rather than the estimated distribution of exposure by institution,

agent, and category). Accordingly, the over-simplified calculation is not protected from effects of differential distribution of agents associated with institution-category combinations (rather than with institution-to-institution or category-to-category changes). In this calculation we ask about the effect of equivalent estimated exposed, rather than estimated exposed, on the "death rates" resulting from prorating institutional deaths and institutional estimated exposed over all five agents in proportion to the total number of uses of each agent in that institution.

Table 1 shows the results of converting the percentages and totals of Table EE-20 in Chapter IV-2 into thousands of EE (some rounding errors are inevitable, but their effect should not be serious). Table 2 shows the results of multiplying these EE by the SMR for the institution (standardizing for age-shock strata) as given in Table 21 of Chapter IV-6, thus converting them into

TABLE 1.--ESTIMATED EXPOSED IN THOUSANDS BY AGENT AND INSTITUTION (CALCULATED FROM TABLE EE-20 IN CHAPTER IV-2)

Institution	H	N-B	C	E	O
1	9.8	6.4	0+	0.3	1.3
2	2.5	0.9	1.0	0.3	0.6
3	1.0	7.3	0.6	0.0+	1.9
4	7.0	2.9	2.4	0.6	2.4
5	3.9	3.1	7.8	0.3	1.5
6	4.8	5.0	0.5	1.0	3.9
7	1.7	1.0	1.6	0.2	1.2
8	22.7	5.5	0.5	15.5	7.7
9	4.2	10.2	2.1	8.1	2.2
10	6.6	3.2	2.6	0.9	0.7
11	5.5	1.9	1.3	2.7	2.2
12	4.8	1.4	3.9	0.2	1.2
13	1.6	0.3	1.2	0.1	1.8
14	2.6	1.7	3.3	0.1	2.2
15	1.6	4.3	4.6	1.3	1.9
16	0.9	4.6	0.5	0.1	2.6
17	1.6	1.3	0.3	4.5	3.8
18	1.6	1.2	1.6	1.1	0.5
19	4.4	4.2	0.9	0+	0.8
20	1.5	2.2	9.2	2.9	5.0
21	11.4	7.4	5.0	0.4	5.1
22	8.3	1.4	3.5	0.5	2.1
23	1.2	1.8	0.9	0	0.3
24	1.6	6.2	0.5	0.1	0.3
25	1.7	0.5	1.0	0.1	1.2
26	9.9	4.9	1.0	0.3	1.3
27	5.8	2.0	2.7	0.5	1.6
28	1.5	1.2	0+	0.3	0.1
29	1.5	0.1	0.1	0.0+	0.5
30	1.3	0.5	0.2	0	0.3
31	2.0	1.0	1.6	0.1	0.2
32	4.2	1.1	1.0	0.1	1.6
33	3.9	3.6	1.3	0.9	3.1
34	1.0	0.1	3.4	0.3	4.0
TOTAL	145.6	100.4	68.1	43.8	67.1

TABLE 2.--MODIFICATION OF TABLE 1 EE BY EEE (BY MULTIPLYING ENTRIES IN THAT TABLE BY SMR FROM TABLE 21 OF CHAPTER IV-6)

Institution	SMR	H	N-B	C	E	O
1	0.564	5.4	3.5	0.0	0.2	0.7
2	1.67	4.2	1.5	1.7	0.5	1.0
3	0.871	0.9	6.2	0.5	0.0	1.6
4	1.17	8.2	3.4	2.8	0.7	2.8
5	1.28	5.0	4.0	10.0	0.4	1.9
6	0.819	3.9	4.1	0.4	0.8	3.2
7	1.55	2.6	1.6	2.5	0.3	1.8
8	0.695	15.8	3.8	0.3	10.8	5.4
9	0.972	4.1	9.9	2.0	7.9	2.1
10	1.25	8.2	4.0	3.3	1.1	0.9
11	1.13	6.2	2.1	1.5	3.1	2.5
12	1.12	5.4	1.6	4.4	0.2	1.3
13	1.44	2.3	0.4	1.7	0.1	2.6
14	0.307	0.8	0.5	1.0	0.0	0.7
15	0.960	1.5	4.1	4.4	1.2	1.8
16	1.16	1.0	5.3	0.6	0.1	3.0
17	0.819	1.3	1.1	0.2	3.7	3.1
18	1.10	1.8	1.3	1.8	1.2	0.6
19	1.24	5.5	5.2	1.1	0.0	1.0
20	0.760	1.1	1.7	7.0	2.2	3.8
21	0.635	7.2	4.6	3.2	0.3	3.2
22	1.25	10.4	1.7	4.3	0.6	2.6
23	0.734	0.9	1.3	0.7	0.0	0.2
24	1.74	2.8	10.4	0.8	0.2	0.5
25	1.59	2.7	0.8	1.6	0.2	1.9
26	0.902	8.9	4.4	0.9	0.3	1.2
27	0.839	4.9	1.7	2.3	0.4	1.3
28	0.353	0.5	0.4	0.0	0.1	0.0
29	1.31	2.0	0.1	0.1	0.0	0.7
30	1.52	2.0	0.8	0.3	0.0	0.5
31	1.34	2.7	1.3	2.1	0.1	0.3
32	0.862	3.6	0.9	1.2	0.1	1.4
33	1.05	4.1	3.8	1.4	0.9	3.3
34	1.08	1.1	0.1	3.7	0.3	4.3
Total		139.0	97.4	69.8	38.0	63.2

values of EEE first by institution and agent, and then by agent.

Table 3 shows the changes in estimated death rates corresponding to changing from EE to EEE (basic death-rate estimates taken from Table 8 of Chapter IV-4). The changes are all small, especially when compared with the change for the total. Except for ether, the changes are by less than 0.0015.

The three differences in death rate found significant in Table 8 of Chapter IV-4, namely, H-C, H-O, and N-B - C, are changed in magnitude by +0.0016, +0.0005, and -0.0012, respectively. If the confidence intervals were to retain their widths, two of these three differences would continue to be significant at 5 percent (and the N-B - O difference, which increases in magnitude by 0.0009, would become significant).

Although it would be very desirable to have at hand the results of one of the more appropriate and more detailed calculations discussed above,

TABLE 3.--APPROXIMATE EFFECTS OF THE PROPOSED ADJUSTMENT

	H	N-B	C	E	O	Totals
Death rate*	0.0202	0.0195	0.0255	0.0227	0.0248	(0.0219)
Total EE**	145.6	100.4	68.1	43.8	67.1	425.0
Corresponding deaths	2941	1956	1737	994	1664	9292
Total EEE**	139.0	97.4	69.8	38.0	63.2	407.4
Equivalent death rate	0.0212	0.0201	0.0249	0.0262	0.0263	(0.0228)
(Change)	(+0.0010)	(+0.0006)	(-0.0006)	(+0.0035)	(+0.0015)	(+0.0009)
Change compared with total	+0.0010	-0.0003	-0.0015	+0.0026	+0.0006	---

*Values from Table 8 of Chapter IV-4.
**Expressed in thousands, from Tables 1 and 2, respectively.

the computations just described suggest quite strongly that adjustment of agent death rates for nonstandard institutional death rates:

(1) would probably not alter the conclusions found above for unadjusted agent death rate, and

(2) might well tend to strengthen those conclusions, rather than weaken them.

There is a real possibility of a concealed effect, involving, say, the details of the three-way distributions of deaths and EE by agent, institution, and category. This concealed effect could be larger than, and of opposite sign to, the effect apparent from Tables 1 through 3, but it does not seem likely that that is the case.

Abstract of Chapter IV-5

The goals of this chapter are to take account of several interfering variables at one time and to reach conclusions about anesthetic comparisons. Estimated death rates are fitted as a function of such interfering variables as age, sex, physical status, and operation; the data are organized into "strata" homogeneous in terms of such estimated death rates; and then, within strata, the death rates associated with the five anesthetics are computed and combined in a standardized death rate (or indirectly standardized mortality ratio).

One set of results is based on the smoothed contingency-table analysis of Chapter IV-3. Roughly, the findings are that cyclopropane and Other have high death rates, ether has low death rates, and halothane and nitrous oxide-barbiturate have intermediate death rates after these multiple adjustments.

A second set of results is based on strata constructed by fitting the variables operation, physical status, age, and length with a cubic polynomial. Roughly, the findings are, again, that cyclopropane and Other have high death rates, ether has low death rates, and halothane and nitrous oxide-barbiturate have intermediate death rates.

A third set of results is based on strata constructed by a cubic polynomial regression, on the two variables age and shock-likelihood index. These are the only results in this chapter for which all operations are considered simultaneously, instead of in the three separate groups: high-, middle-, and low-death-rate operations. The results in this analysis are similar to those of the previous two, in that the order of adjusted death rates from highest to lowest is: Other, cyclopropane, halothane, nitrous oxide-barbiturate, and ether.

These studies do not carry with them estimates of sampling reliability. Some clue as to the reality of the results was obtained by identifying the hospitals in which halothane and cyclopropane were each used in at least 20 percent of all surgical procedures (in the middle-death-rate group). There were 11 such hospitals. Adjusted death rates for halothane and cyclopropane were calculated in those hospitals; in 10 of the 11, halothane had a lower adjusted death rate than cyclopropane. That is a good indication of the reality of the difference. Of the same 11 hospitals, eight had lower halothane death rates than cyclopropane death rates for the high-death-rate operations.

CHAPTER IV-5. ANALYSIS BY REGRESSION METHODS

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Chapter IV-2 gave a general description of the data, exhibiting how death rates depended not only on the anesthetic, but also on such "independent variables" as age, sex, and physical status. Some effort to purge agent contrasts of the interfering effects of these other variables was undertaken by computing standardized death rates, standardizing for each variable separately. That chapter explained the desirability of adjusting for several variables at once. Chapter IV-4, dealing with smear-and-sweep analysis, addressed the standardization problem using a particular mode of attack. In Chapter IV-3, the smoothed contingency-table analysis fitted a class of statistical models to the data, enabling death rates for individual cells in the complex cross-classification to be estimated; those estimates were not merely based on the cases that belonged to particular cells, but "borrowed strength" from other portions of the data. This chapter will partake of some of the nature of both of the immediately preceding ones. It will resemble Chapter IV-3 in that statistical models will be fitted, and it will resemble Chapter IV-4 in that over-all comparisons among anesthetic agents will be made after adjustment for several variables.

The general scheme is as follows: A model for estimating the probability of death as a function of such variables as operation, length, and age is proposed. Then the model is fitted to the data by some estimation procedure. This calculation associates an estimated death rate with each cell of the cross-classification of the data. These estimated death rates tend to be more stable than individual cell rates, because they are based on more of the data. The cells are then coalesced into "strata," in such a way that cells with the lowest death rates fall into the first stratrum, cells with the next lowest death rates into the second, and so on. These strata are the basis for the calculation of standardized death rates for each anesthetic agent. In this manner, it is to be expected that much of the effect of interfering variables is removed from the comparisons of death rates following the several agents.

STRATA DERIVED FROM SMOOTHED CONTINGENCY-TABLE ANALYSIS

In Chapter IV-3, the method of fitting death rates for the high-, middle-, and low-death-rate operation groups, as well as for the cholecystectomies, was described. Table 3 of that chapter summarizes the fitting procedure. To establish strata, the cells of the contingency table were swept up in the order determined by the fitted rates into 10 categories (or as close to 10 as the data permitted), in such a manner that the categories had equal numbers of deaths plus estimated exposed. The results of the standardizing with respect to these categories are displayed in Tables 1 and 2. In Table 1, the directly standardized rates are shown for the low-death-rate operations, for the middle-death-rate operations (both four-variable and five-variable fits have been used), for the high-death-rate operations, and for the cholecystectomies. Table 2 displays indirectly standardized mortality ratios. In the low-death-rate group, nitrous oxide-barbiturate and ether have the low death rates, halothane and cyclopropane have approximately equal rates (higher than for nitrous oxide-barbiturate and ether), and Other has the highest death rate. In the middle-death-rate operations, whether four or five variables are fitted, ether is lowest, halothane and nitrous oxide-barbiturate are approximately equal and a little higher, and cyclopropane and Other are much higher, with cyclopropane the highest. In the high-death-rate operations, ether and halothane are nearly equal and lowest, nitrous oxide-barbiturate is next, and cyclopropane and Other are approximately equal and highest. In the cholecystectomies, all rates are between 0.020 and 0.029, increasing in the order halothane, ether, cyclopropane, nitrous oxide-barbiturate, and Other. These analyses are all based on the main fitting procedure used in Chapter IV-3, in which anesthetic agent was one of the variables fitted.

We can reasonably ask whether some contamination of the findings may result from first

TABLE 1.--DIRECTLY STANDARDIZED RATES; STRATA BASED ON CONTINGENCY-TABLE FITTING*

Group	Agent					
	H	N-B	C	E	O	All
Low	0.0025	0.0016	0.0025	0.0018	0.0033	0.0022
Middle, model B	0.0195	0.0195	0.0279	0.0179	0.0255	0.0221
Middle, model A	0.0193	0.0197	0.0278	0.0177	0.0257	0.0221
High (A)	0.0844	0.0914	0.1097	0.0811	0.1079	0.0933
Chole	0.0203	0.0262	0.0251	0.0230	0.0284	0.0238

*Strata defined by sweepup (on D+EE into 10 categories) in order of death rate, as fitted by methods described in Table 3 of Chapter IV-3.

TABLE 2.--INDIRECTLY STANDARDIZED MORTALITY RATIOS; STRATA BASED ON CONTINGENCY-TABLE FITTING

Group	Agent				
	H	N-B	C	E	O
Low	1.12	0.73	1.13	0.82	1.45
Middle, model B	0.88	0.88	1.26	0.81	1.15
Middle, model A	0.88	0.89	1.26	0.80	1.16
High (A)	0.91	0.98	1.17	0.85	1.12
Chole	0.86	1.10	1.06	0.97	1.20

TABLE 3.--DIRECTLY STANDARDIZED RATES; STRATA BASED ON CONTINGENCY-TABLE FITTING (without anesthetic)

Group	Agent					
	H	N-B	C	E	O	All
Low	0.0023	0.0016	0.0026	0.0018	0.0034	0.0022
Middle, model B	0.0195	0.0197	0.0277	0.0178	0.0257	0.0221
Middle, model A	0.0192	0.0197	0.0277	0.0185	0.0258	0.0221
High (A)	0.0854	0.0923	0.1258	0.0830	0.1084	0.0933
Chole	0.0205	0.0257	0.0253	0.0244	0.0318	0.0238

TABLE 4.--INDIRECTLY STANDARDIZED MORTALITY RATIOS; STRATA BASED ON CONTINGENCY-TABLE FITTING (without anesthetic)

Group	Agent				
	H	N-B	C	E	O
Low	1.07	0.73	1.18	0.80	1.48
Middle, model B	0.89	0.89	1.26	0.80	1.15
Middle, model A	0.87	0.89	1.26	0.82	1.16
High (A)	0.91	0.98	1.19	0.80	1.12
Chole	0.86	1.06	1.05	0.93	1.13

using anesthetic in constructing the strata and then making comparisons between anesthetics within strata. Because of unease about this point, the same contingency-table analysis was fitted with agent not being used as a fitting variable. The results appear in Tables 3 and 4. The presentation here is of the same form as in the previous tables. The numeric values found are remarkably close to those obtained when anesthetic was used as a fitting variable. Indeed, there are no qualitative differences worth noting.

It is interesting to speculate how this similarity of findings occurs. The following plausible explanation may contain the germ of the correct idea. Differences between death rates following the anesthetics are small enough so that even with very numerous data they are hard to exhibit and estimate accurately. At the same time, the other variables used in the fitting are quite influential. Operation, physical status, and age all carry great variability in death rates. It is then to be expected that estimates based on a regression model (or on some other form of fitting) that uses all variables except anesthetic will scarcely be modified when the relatively uninfluential variable, anesthetic agent, is adjoined to them as a further predictor. If that is true, it must follow that strata based on the fitted values will have to be very similar for the two modes of fitting, and the standardized death rates based on nearly the same strata will necessarily have nearly the same values.

STRATA DEFINED BY REGRESSION ANALYSIS

The mode of fitting used above can be regarded as a regression method of fitting the logarithm of the death rate, but this use of regression does not take account of the ordered or metric properties of the predictor variables. Rather, it is regression in the sense that the analysis of variance is regression. Large numbers of constants had to be fitted, and it required considerable effort to solve the computational problems involved in the fitting. An alternative regression analysis now to be described is a substantially smaller computational task, and therefore seemed worth developing. There are several steps: (1) define the variables for purposes of regression, (2) choose a model, (3) fit the model, (4) sweep up cases into strata, and (5) construct the standardized rates using those strata.

The main body of this section concerns the regression analysis using the variables operation, physical status, length, and age. Of these variables, only length and age are naturally quantitative variables as they stand. Physical status consists of four ordered categories for elective procedures and three ordered categories for emergency procedures, and the rearrangement of these into a single quantitative variable is, in some measure, arbitrary. The same is even truer of operation. The principle adopted was to arrange the categories of the variable in such a manner that the death rate was an increasing function of the category assignment. That provision, although it may be sensible, certainly introduces a nonstandard character to "regression." Later in this

section, a "pure regression analysis" is described, in which the two variables used are age and estimated propensity for shock; that analysis is free of the novel and arbitrary feature just described. A final discussion gives some consideration to the sampling stability of the findings.

The ORLA Analysis

Throughout this section we use the variables operation, physical status (risk), length, and age (sometimes the set is abbreviated "ORLA") to construct strata. We have dealt separately with the high-, middle-, and low-death-rate operation fractions of the entire body of data. The general approach has been to find a polynomial regression for one of the fractions using these interfering variables; to calculate for each case the estimated probability of death, considering age, operation, physical status, and length, but ignoring the anesthetic; and then to collect (sweep up) all the cases in order of this estimated probability into 10 or 15 approximately equal-sized strata. Once the strata have been established, we calculate standardized death rates for the anesthetic agents. The summary findings in this section are presented in Table 5, which shows that, whether we consider the standardized rates themselves or the indirectly standardized mortality ratios, cyclopropane and Other have higher death rates than halothane, nitrous oxide-barbiturate, and ether, and that ether is the best, at least in the middle- and low-death-rate groups. Whether these appearances can be trusted depends in part on how uniformly they hold up from hospital to hospital. Thus, the reader should, at this time, reserve his acceptance of the apparent conclusions implied by the table. The question of stability across institutions is discussed in the final section of this chapter.

It is possible that the category "Other" has been unfairly penalized to the illusory advantage of the remaining agents. It could have happened in this way: Wherever two or more major agents are applied together, the anesthetic has been classified as "Other." If there is a tendency for a patient in trouble on one of these agents then to be switched over to another, the high death rate associated with such troubles would never be charged to the original anesthetic, but rather would be charged to Other. To investigate the degree to which this possible bias may be operating, we have done some calculations in which a patient who ever received halothane is charged to halothane, a patient who ever received cyclopropane is charged to cyclopropane, and so on.* In these calculations, we used exactly the same strata as in Table 5, but defined anesthetic as just described. The resulting directly standardized rates are displayed in Table 6. The principal effect of using the overlapping definition of anesthetic agents is to raise the standardized rates for Other in all three groups, and to affect the rates for any of the agents only a little. It would thus appear that those surgical procedures in which major agents have been used in combination are not especially "rich in deaths," but that, in fact, when they are removed from the category "Other," the residuum in that classification has an even higher death rate than before. Thus, we may dismiss the possibility of bias in question as erroneous; the bias actually favored Other. (A detailed presentation of the steps that led to the development of Table 5 appears as Appendix 1.)

*This leads to the association of some cases with two, or even three or four, of the anesthetic agents as now defined.

Regression on Age and Shock-Likelihood Index

Age appeared in seven categories (see Appendix 1). The variable shock-likelihood index (SLI) has five ordered categories of increasing conjectured propensity for shock, plus an "unknown" category. Operation and anesthetic risk (physical status) determine the value assigned to this variable. When anesthetic risk is "unknown" the SLI is also "unknown." "Unknown" was used as the first of the six SLI categories. (Details relating to SLI are given more fully in Chapter IV-7.)

Estimated logit ($\log(p/(1-p))$, where p is the death rate) was represented as a cubic polynomial (involving all terms) in age and SLI, and a cubic in SLI was fitted separately to the first age category. The 42 cells were then swept up in order of estimated logit into 10 categories approximately equinumerous in terms of deaths-plus-randoms. Standardized death rates were then calculated (Table 7). The results are qualitatively similar to those we have seen for the middle-death-rate operations: ether lowest, halothane and nitrous oxide-barbiturate next, and cyclopropane and Other highest; Other is higher than cyclopropane. At the same time, the magnitude of the halothane-cyclopropane contrast is very much lower than it was for the middle-death-rate operations. Halothane is notable in having, to the accuracy shown, the average over-all death rate of the Study.

Sampling Stability

Estimates of death-rate comparisons, such as those in Tables 5, 6, and 7, necessarily contain a sampling error, and it is desirable to be able to estimate its size. If it is small, compared with the differences, we would be inclined to trust the differences more than if it were large. Unfortunately, the methods of analysis used here generally do not admit of known estimates of sampling error, but some useful, if fragmentary, insight into the problem can be obtained.

Consider the difference in rates for halothane and cyclopropane, the two most widely used anesthetics in the National Halothane Study. Their standardized death rates differ appreciably, no matter what analysis we refer to, cyclopropane having the higher death rate. On the one hand, if this pattern is not merely an over-all trend, but

TABLE 5.--COMPARISON OF ANESTHETIC AGENTS BY STANDARDIZATION ON REGRESSION-BASED STRATA*

Group	Agent					
	H	N-B	C	E	O	All
Direct:						
High	0.0839	0.0903	0.1166	0.0988	0.1085	0.0934
Middle	0.0204	0.0194	0.0275	0.0173	0.0256	0.0221
Low	0.00228	0.00187	0.00271	0.00166	0.00324	0.00228
Indirect MR:						
High	0.892	0.963	1.199	0.912	1.128	
Middle	0.921	0.875	1.236	0.778	1.139	
Low	0.995	0.820	1.184	0.708	1.395	

*The regressions were cubic, on variables operation, physical status, length, and age. Separate regressions were fitted for the three groups: high-, middle-, and low-death-rate operations. In each case, 10 strata, approximately equinumerous in terms of death-plus-randoms, were constructed by pooling cases in order of regression estimate of death rate.

TABLE 6.--COMPARISON OF AGENTS (OVERLAPPING DEFINITION*) BY DIRECTLY STANDARDIZED DEATH RATES

(Regression-based strata)

(Corresponding figures from Table 5 in parentheses)

Group	Agent					
	H	N-B	C	E	O+	All
High	0.0822 (0.0839)	0.0822 (0.0903)	0.1038 (0.1166)	0.0941 (0.0988)	0.1710 (0.1085)	0.0880 (0.0934)
Middle	0.0209 (0.0204)	0.0179 (0.0194)	0.0261 (0.0275)	0.0193 (0.0173)	0.0335 (0.0256)	0.0210 (0.0221)
Low	0.00253 (0.00228)	0.00205 (0.00187)	0.00276 (0.00271)	0.00226 (0.00166)	0.00395 (0.00324)	0.00232 (0.00228)

*This table uses exactly the same strata as in Table 5; it differs in that any procedure involving halothane (which might be classed as "halothane" or "Other" in the earlier table) is now counted as "halothane," etc.

+The frequencies in the modified "Other" category become: high, 506 deaths and 1935 EE; middle, 901 deaths and 30,437 EE; and low, 74 deaths and 14,321 EE.

TABLE 7.--DIRECTLY STANDARDIZED DEATH RATES BASED ON AGE-SHOCK REGRESSION STANDARDIZATION*

(All operations, "unknown" shock patients included as first of six categories)

	Agent					
	H	N-B	C	E	O	All
Death rate	0.0193	0.0172	0.0216	0.0152	0.0233	0.0193
Mortality ratio	1.00	0.892	1.12	0.788	1.29	--

*Swept to 10 categories on deaths-plus-randoms.

recurs in virtually all hospitals, we would be inclined to conclude that the finding would emerge again if yet other hospitals were studied. On the other hand, if cyclopropane were superior in many hospitals and halothane were superior in many others, we would put little confidence on the overall difference exhibited in the aggregate figures.

Among the 34 hospitals in the Study, 11 used halothane and cyclopropane each in at least 20 percent of their operations. These 11 hospitals were studied to see whether the apparent superiority of halothane over cyclopropane was stable across

TABLE 8.--ANESTHETIC DEATH RATES*

(Standardized by strata from ORLA logit regression in 11** institutions using halothane and cyclopropane each in at least 20 percent of procedures)

Inst.	Standardized death rates						Indirectly standardized mortality ratios				
	Agent						Agent				
	H	N-B	C	E	O	All	H	N-B	C	E	O
5	0.0379	0.0485	0.0431	0.3081	0.0776	0.0413	0.89	1.04	0.93	2.14	1.18
7	0.0441	0.0437	0.0510	0.2151	0.0657	0.0527	0.79	0.74	0.88	2.40	1.21
12	0.0240	0.0183	0.0260	0.3037	0.0386	0.0247	0.93	0.57	1.00	4.15	1.26
13	0.0342	0.0317	0.0630	0.0161	0.0191	0.0292	1.05	0.93	1.87	0.44	0.61
14	0.0095	0.1530	0.0168	0.4353	0.0107	0.0089	0.79	0.94	1.27	1.55	0.82
18	0.0263	0.0347	0.0366	0.0106	0.0466	0.0312	0.82	1.11	1.15	0.29	1.37
21	0.0143	0.0156	0.0199	0.1198	0.0182	0.0154	0.88	0.86	1.22	2.79	1.04
22	0.0197	0.0272	0.0237	0.0845	0.0931	0.0238	0.79	1.01	0.93	0.52	2.32
23	0.0081	0.0116	0.0242	None	0.0206	0.0114	0.72	0.96	1.13	--	2.15
25	0.0613	0.0761	0.0943	0.2020	0.0929	0.0811	0.74	0.82	1.14	1.75	1.12
31	0.0258	0.0213	0.0185	0.0195	0.1276	0.0205	1.02	0.99	0.86	0.42	2.39

*Middle-death-rate operations only.

**Reference population is all middle-death-rate operations in the particular institution.

hospitals. Table 8 presents the data on that issue for the middle-death-rate operations. The two halves of the table show directly standardized death rates and indirectly standardized mortality ratios based on 10 strata swept up in terms of deaths-plus-randoms after polynomial regression on risk, length, operation, and agent for the middle-death-rate operations. In all but institution 31, halothane looks better than cyclopropane. It may also be seen that the smoothness in the total data is lacking when we go to the individual hospital; indeed, the most regular finding in the table is the halothane-cyclopropane contrast (which is natural, inasmuch as the hospitals were selected for study because the data were relatively ample).

When the analysis in Table 9 was done for the same 11 hospitals on the high-death-rate operations, there was far less uniformity than in Table 8. The data were sufficiently meager so that nine of the 55 cells did not even permit defining standardized death rates. Although these institutions had been selected for the frequency with which they used both halothane and cyclopropane, there appears to be considerable variability even for these agents. In eight of the hospitals, cyclopropane had a higher standardized death rate than did halothane; in the other three hospitals, halothane had the higher rate. It appears that no clear statement can be made from this analysis as to how halothane and cyclopropane compare, on the average, for the high-death-rate operations.

TABLE 9.--ANESTHETIC DEATH RATES*

(Standardized by strata from ORLA logit regression in 11 institutions using halothane and cyclopropane each in at least 20 percent of procedures)

(a) Directly Standardized Death Rates**

Institution	Agent					
	H	N-B	C	E	O	All
5	0.096	0.498	0.144	0.324	0.331	0.100
7	0.188	--	0.130	0.508	0.272	0.143
12	0.263	0.376	0.063	--	0.112	0.066
13	0.007	--	0.123	0.001	0.018	0.024
14	0.002	--	0.110	--	--	0.001
18	0.057	0.021	0.088	0.037	0.136	0.072
21	0.041	0.256	0.081	0.500	0.272	0.044
22	0.065	0.140	0.084	0.039	0.166	0.074
23	0.013	0.011	0.110	--	0.006	0.011
25	0.054	0.087	0.150	0.802	0.183	0.137
31	0.138	0.102	0.088	--	--	0.089

(b) Indirectly Standardized Mortality Ratios

Institution	Agent					
	H	N-B	C	E	O	All
5	0.66	1.51	0.91	0.83	1.31	1.0
7	0.93	--	0.81	0.87	1.59	1.0
12	1.97	0.84	0.56	--	0.80	1.0
13	0.34	--	3.68	77.30x	0.71	1.0
14	0.30	--	4.04	--	--	1.0
18	0.85	0.17	1.23	0.43	1.95	1.0
21	0.60	1.65	1.48	2.21	0.90	1.0
22	0.85	0.95	0.99	0.43	1.61	1.0
23	0.98	0.93	1.29	--	--	1.0
25	0.31	0.70	1.05	3.10	1.29	1.0
31	0.89	1.33	0.88	--	1.30	1.0

*High-death-rate operations only.

**The category any particular observation falls into is based on 10 categories with approximately equal numbers of deaths-plus-randoms made from the estimated logit of the observations of all high-death-rate operations in all 34 institutions.

x Undefined.

APPENDIX 1 TO CHAPTER IV-5

REGRESSION MODEL USED IN CHAPTER IV-5

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We proposed to develop strata based on the variables age, length, operation, and physical status. The categories that we used for these variables are listed below. The categories for each variable are ordered and the order is exhibited in the listing.

Age: 0-9; 10-39; 40-49; 50-59; 60-69; 70-79; and 80+ (cases with unknown age omitted).
Risk: 1,2,5; unknown; 3,4,6; and 7.
Length: 1-28; 29-58; 59-118; 119-238; 239-388; and 389 and over (cases with unknown length omitted).

Operation had to be coded differently for high-, middle-, and low-death-rate groups, because different operations appear there. For high, the categories were, in order of death rate: large bowel (code 48), exploratory laparotomy (44), craniotomy (12), and heart with pump (33). For middle, the five categories were:

1 - 2, 4, 6, 7, 8, 9, 10, 15, 20, 21, 23, 30, 32, 40, 50, 54, 62, 63, 66, 68, 71, 80, 81, 84, 85, 87, 89, 92, 95, and 99;
2 - 5, 16, 25, 39, 56, 58, 70, 75, 76, 77, and 98;
3 - 26, 28, 41, 42, 51, 88, and 93;
4 - 13, 17, 27, 34, 36, 43, 45, 46, and 87; and
5 - 22, 47, 52, 57, 59, 67.

For low, the categories were, in order of increasing death rate: mouth (1), eye (3), and dilatation and curettage (60); hysterectomy (65); herniorrhaphy (55) and cystoscopy (73); and plastic surgery (90). It should be observed that neither risk nor operation is truly a metric variable; instead, the value of the independent variable has been assigned after study of its relation to the dependent variable.

We set out to fit a polynomial model of no more than third degree in all variables simultaneously for the expected logit of the death rate. A key question was how many of the possible polynomial terms could reasonably be omitted and which ones presumably should definitely be included. At the beginning, we constructed row and column arrays using two variables at a time and found where there appeared to be important interactions. We then fitted full cubic polynomials to the two-way tables, risk × length and risk × age, and to the three-way table, age × length × risk, and studied which terms appeared to be droppable in the resulting regressions.

Age, an important variable, has an erratic relation to death rate, in that there is a sharp drop from the rate at 0-9 to the rate at 10-19, after which death rate steadily increases. Because of that, a separate fit was made for the first age category, a_1. Three of the coefficients (of the 24 fitted) were estimated from both the $a = a_1$ and the $a \neq a_1$ data; these were the coefficients for $r \times o$, r^3, and $\ell^2 r$.

We finally fitted the following polynomials of the third degree:

$$\begin{aligned} E(\text{logit } p) = {} & \mu + b_1^1 a + b_2^1 \ell + b_3^1 r + b_4^1 o \\ & + b_{12}^2 a\ell + b_{13}^2 ar + b_{14}^2 ao + b_{23}^2 \ell r \\ & + b_{24}^2 \ell o + b_{34}^2 ro + b_2^2 \ell^2 + b_3^2 r^2 \\ & + b_4^2 o^2 + b_3^3 r^3 + b_{23}^3 \ell^2 r, \end{aligned}$$

where $a \neq a_1$, and

$$\begin{aligned} E(\text{logit } p) = {} & \mu_1 + c_2^1 \ell + c_3^1 r + c_4^1 o + c_2^2 \ell^2 \\ & + c_3^2 r^2 + c_4^2 o^2 + c_{24}^2 \ell o + b_{34}^2 ro \\ & + b_3^3 r^3 + b_{23}^3 \ell^2 r, \end{aligned}$$

where $a = a_1$.

In fitting this model we proceeded iteratively and used weights $w_\alpha = n_\alpha \hat{p}_\alpha (1-\hat{p}_\alpha)$, where n_α = estimated exposed plus 50 (or, in some of the subproblems, plus deaths).

It should be remarked that the weights used could be defended better if the observations had been truly binomial. In the actual case, the value of n is itself an estimated quantity and this should ideally call for the use of different weights. Although the theory for fitting with the appropriate

TABLE 1.--STANDARDIZED DEATH RATES (ALL AGENTS, MIDDLE-DEATH-RATE OPERATIONS)
(Strata from logit regression I on ORLA; various modes of sweepup)

Categories	Sweepup	Agent					
		H	N-B	C	E	O	All
10	Deaths	0.0205	0.0199	0.0270	0.0177	0.0254	0.0221
	EE	0.0198	0.0189	0.0282	0.0169	0.0263	0.0221
	D+R	0.0204	0.0194	0.0275	0.0173	0.0256	0.0221
15	Deaths	0.0208	0.0202	0.0270	0.0179	0.0256	0.0221
	EE	0.0201	0.0193	0.0278	0.0166	0.0260	0.0221
	D+R	0.0205	0.0196	0.0274	0.0173	0.0256	0.0221

TABLE 2.--STANDARDIZED DEATH RATES FOR MIDDLE-DEATH-RATE OPERATIONS (VARIOUS REFERENCE POPULATIONS)
(Strata from logit regression I on ORLA; sweepup to 10 categories on D+R)

Reference population	Agent					
	H	N-B	C	E	O	All
H	0.0173	0.0164	0.0236	0.0145	0.0221	0.0188
N-B	0.0180	0.0171	0.0244	0.0151	0.0229	0.0195
C	0.0252	0.0242	0.0339	0.0219	0.0313	0.0274
E	0.0222	0.0208	0.0297	0.0185	0.0276	0.0238
O	0.0244	0.0232	0.0326	0.0209	0.0300	0.0263
All	0.0204	0.0194	0.0275	0.0173	0.0256	0.0221

TABLE 3.--INDIRECTLY STANDARDIZED MORTALITY RATIOS, MIDDLE-DEATH-RATE OPERATIONS (ALL AGENTS)
(Strata from logit regression I on ORLA; various modes of sweepup)

Categories	Sweepup	Agent					
		H	N-B	C	E	O	All
10	Deaths	0.927	0.899	1.196	0.780	1.133	1.000
	EE	0.899	0.857	1.275	0.768	1.182	1.000
	D+R	0.921	0.875	1.236	0.778	1.139	1.000
15	Deaths	0.931	0.903	1.186	0.778	1.133	1.000
	EE	0.910	0.877	1.252	0.754	1.165	1.000
	D+R	0.926	0.885	1.228	0.770	1.130	1.000

TABLE 4.--INDIRECTLY STANDARDIZED MORTALITY RATIOS, FOR MIDDLE-DEATH-RATE OPERATIONS (VARIOUS REFERENCE POPULATIONS)
(Strata from logit regression I on ORLA; sweepup to 10 categories on D+R)

Reference population	Agent					
	H	N-B	C	E	O	All
H	1.000	0.949	1.345	0.835	1.230	1.083
N-B	1.053	1.000	1.401	0.890	1.293	1.140
C	0.733	0.698	1.000	0.624	0.921	0.802
E	1.190	1.128	1.548	1.000	1.435	1.276
O	0.781	0.745	1.084	0.673	1.000	0.862
All	0.921	0.875	1.236	0.778	1.139	1.000

weights was worked out, it was not applied to these data.

Each of the pigeonholes (840 for the middle-death-rate operations) could now have associated with it an estimated logit value obtained by combining the values of *i*, a, r, and o for the pigeonhole with the fitted values of the regression coefficients. The pigeonholes were then listed in estimated logit order, and cumulative deaths, cumulative estimated exposed, and cumulative deaths-plus-randoms were printed out; then by hand the ordered pigeonholes were swept up into 10 categories approximately equinumerous in each of the three modes and again into 15 categories approximately equinumerous in each of the three modes. Then for each of the six methods of sweepup into categories, standardized death rates for all agents were constructed, using as standardizing populations each of the five agent populations and the combined population. Indirectly standardized mortality ratios were also computed, using each of the six kinds of category systems and again the six reference populations.

Table 1 shows that, as far as the six methods of sweepup are concerned, the findings are all about the same: ether has the lowest standardized death rate, halothane and nitrous oxide-barbiturate are next, with approximately equal rates, and finally cyclopropane and Other are the worst, also with approximately equal rates. It is noteworthy that in all six rows of that table the rank order of the agent death rates is the same.

Table 2 involves the 10-category, deaths-plus-randoms sweepup method,* and shows the standardized death rates for the agents, using various reference populations. Qualitatively, the conclusions are as before, i.e., in all six rows of the table the rank order among the five anesthetic agents is exactly the same, and exactly the same as that found in the first table. However, the numeric values of the standardized death rates are quite different for various reference populations. In particular, it can be seen from the right-hand column that halothane and nitrous oxide-barbiturate have the lowest standardized death rates, and that Other and cyclopropane have the highest, with ether intermediate. The position of ether is curious, for it appears to mean that the ether population is a relatively high-death-rate one, a conclusion we must bear in mind (and find contradicted) as we go to the second set of tables.

Tables 3 and 4 present findings in terms of indirectly standardized mortality ratios. The former exhibits these ratios with all middle-death-rate operations as the reference population for the six methods of sweepup. The findings are consonant with those for the standardized death rates, i.e., the rank order of the agents is, in every row, identical with what we have previously observed, and there is good qualitative agreement from row to row. Table 4 uses the 10-category deaths-plus-randoms sweepup and various reference populations; again, in every population, the order among the agents is exactly as we have previously found 18 times. But in this case, when we study the right-hand margin, it appears that ether has the most favorable population, halothane and nitrous oxide-barbiturate the next most favorable, and cyclopropane and Other the least favorable. Note the curious

*Reasons for preferring this sweepup method are sketched in Appendix 2.

change in the role of ether: it was intermediate when looked at in terms of standardized death rate, and is now most favorable when studied in terms of indirectly standardized mortality ratios.

These two sets of tables are a highly condensed summary of all the middle-death-rate data in terms of regression stratification, and suggest that halothane and nitrous oxide-barbiturate are anesthetics with lower death rates, that cyclopropane and Other are anesthetics with higher death rates, and that ether may have the lowest rate of all for these operations. Furthermore, these conclusions appear to hold for various methods of sweepup, various reference populations, and the use of either direct or indirect rates.

APPENDIX 2 TO CHAPTER IV-5

REMARKS ON SWEEPUP RULES

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Figures 1 and 2 show (for 10 and for 15 categories) the percentage of "cases"* swept up into categories having predicted logit less than or equal to the value indicated on the abscissa.

The graph is interpreted as follows: Look at the 10-categories graph (Fig. 1). Consider the number -3.0, shown on the horizontal axis; that is the logit transform of p = 0.047. The polygonal curve labeled "deaths" has a height of 0.2 at -3.0; this means that 20 percent of the deaths lay in categories (the first two) with estimated death rates smaller than 0.047. The next "curve" (deaths + randoms) stands at 0.6 and implies that the first six categories (containing six-tenths of the observations) had estimated death rates less than 0.047. The highest curve (EE) stands at 0.8 and indicates that 80 percent of the exposures to anesthesia in the Study belonged to combinations of operation, physical status (risk), length, and age estimated to carry a death rate less than 0.047.

*"Case" defined for the three graphs: deaths, deaths plus randoms, and EE.

From the graphs it appears that:

(1) D + R picks cases up in a way intermediate between the other two modes;
(2) the three modes compare in about the same way for 10 as for 15 categories; and
(3) pickup on deaths gives the smallest variety of estimated death rates, i.e., it appears to lead to coarser strata (the first death stratum corresponds to the first nine EE strata in the case of 15 categories).

Primarily because of the last point, sweepup on death may be least desirable. One may prefer D + R to EE, because it gives a finer stratification in the high-death-rate zone, and an equally fine one elsewhere.

Table 1 gives the data from which the graphs were made. The sweepup was done by hand from a printout of the 840 ORLA cells (in logit order) that showed cumulative D, D + R, and EE.

TABLE 1.--TABULATION FOR SWEEPUP GRAPHS IN ORLA REGRESSION I

	Deaths				Estimated exposed			
	10 categories		15 categories		10 categories		15 categories	
1	-4.04	0.1	-4.50	0.065	-7.53	0.087	-7.85	0.071
2	-3.27	0.2	-3.73	0.133	-6.92	0.188	-7.37	0.171
3	-2.72	0.3	-3.27	0.2	-6.47	0.291	-6.81	0.196
4	-2.32	0.403	-2.91	0.27	-5.84	0.396	-6.52	0.282
5	1.99	0.5	-2.61	0.334	-5.29	0.5	-6.23	0.336
6	-1.72	0.601	-2.33	0.402	-4.68	0.596	-5.79	0.405
7	-1.46	0.699	-2.09	0.467	-4.09	0.7	-5.45	0.465
8	-1.15	0.801	-1.87	0.535	-3.46	0.8	-5.16	0.533
9	-0.834	0.9	-1.72	0.601	-2.48	0.898	-4.68	0.596
10	-0.067	1.0	-1.53	0.667	-0.067	1.0	-4.37	0.663
11			-1.42	0.735			-3.93	0.733
12			-1.15	0.801			-3.46	0.8
13			-0.971	0.867			-2.85	0.868
14			-0.655	0.934			-2.05	0.933
15			-0.067	1.0			-0.067	1.0

	Randoms + Deaths									
	10 categories					15 categories				
1	-7.37	0.12	6	-3.27	0.6	1	-7.5	0.0615	9	-3.27	0.6
2	-6.47	0.203	7	-2.54	0.7	2	-6.9	0.132	10	-2.76	0.665
3	-5.74	0.297	8	-1.87	0.8	3	-6.47	0.203	11	-2.33	0.732
4	-4.75	0.402	9	-1.34	0.898	4	-5.85	0.272	12	-1.87	0.798
5	-4.04	0.5	10	-0.067	1.0	5	-5.34	0.333	13	-1.52	0.867
						6	-4.78	0.4	14	-1.11	0.934
						7	-4.35	0.464	15	-0.068	1.0
						8	-3.80	0.532			

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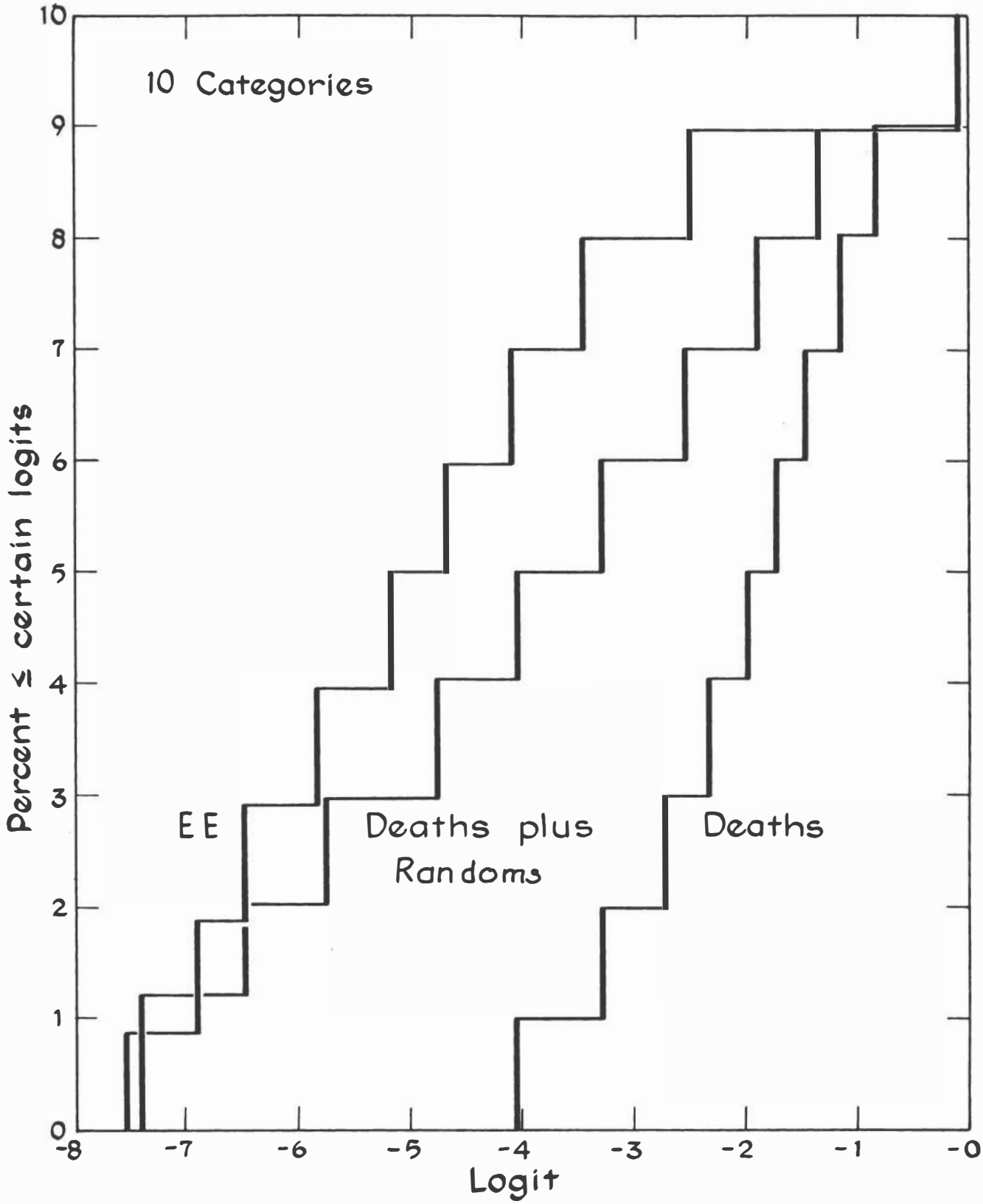

Figure 1.--For 10 categories: Percentage of cases swept up into categories having predicted logit less than or equal to value indicated on abscissa.

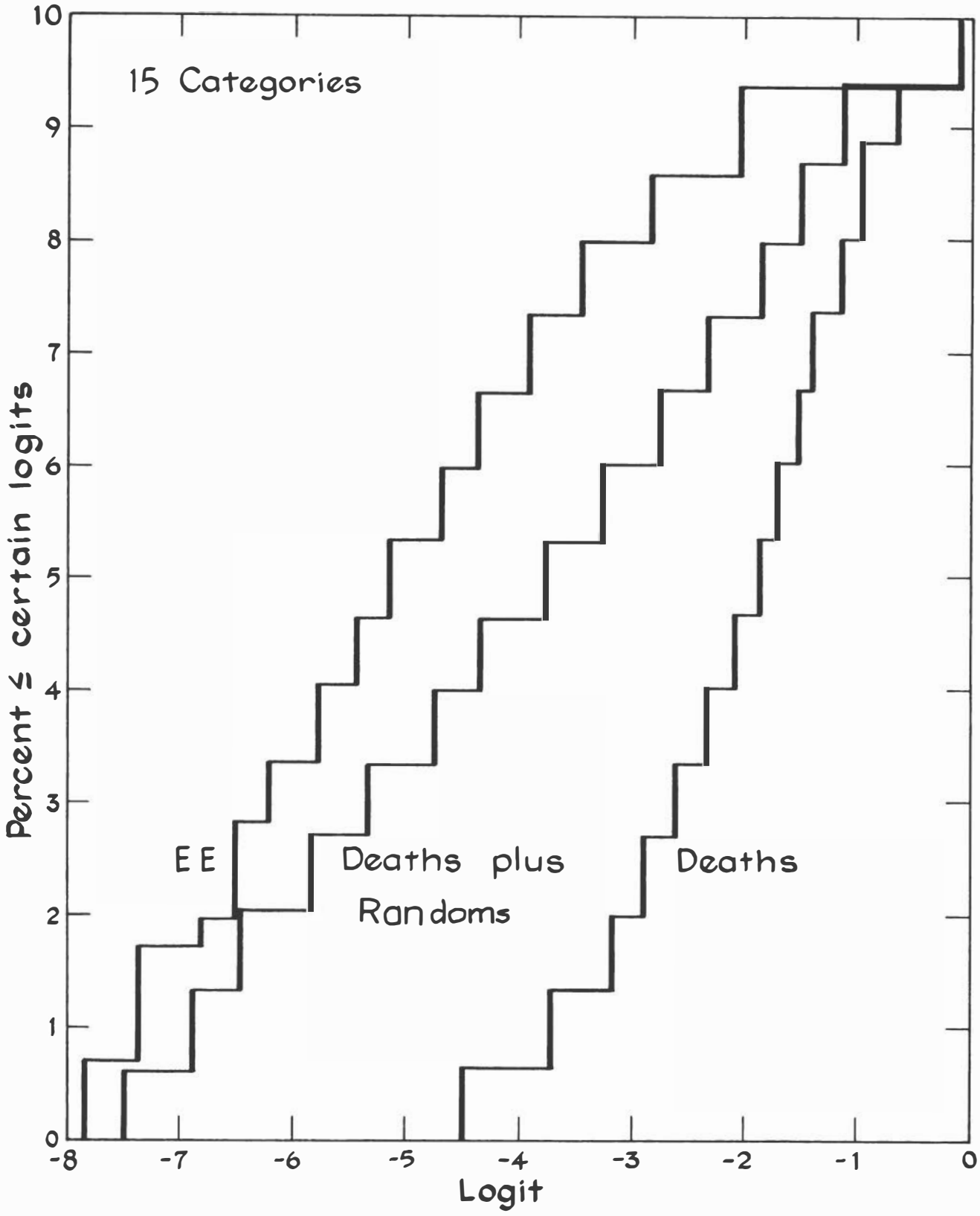

Figure 2.--For 15 categories: Percentage of cases swept up into categories having predicted logit less than or equal to value indicated on abscissa.

Abstract of Chapter IV-6

In this chapter, comparison of anesthetic agents after multiple adjustment for interfering variables is attempted by another scheme of stratum construction. In the cross-classification of the data formed from the interfering variable categories, the over-all death rate can be calculated for each cell. Cells are then aggregated in death-rate order into a number of strata. Anesthetic death rates within strata can be determined and death rates standardized against strata can be calculated. That was the approach used in this chapter.

The first body of results is based on the cross-classifications used in Chapter IV-3. Roughly, cyclopropane and Other had high death rates, ether had low death rates, and halothane and nitrous oxide-barbiturate had intermediate death rates.

The second body of results began with the cross-classification of the data on the variables age, length, physical status, and operation. The findings were substantially the same.

A third body of results used the cell aggregation from the two-way classification by age and shock-likelihood index (SLI); again, Other and cyclopropane had high death rates, ether had low death rates, and halothane and nitrous oxide-barbiturate had intermediate death rates. This was the only set of results in this chapter that treated all the operations as a single body, rather than dividing them into high-, middle-, and low-death-rate groups.

The similarity in findings between strata based on aggregation (in this chapter) and findings based on strata obtained by fitting death rates was investigated. The two sets of strata are very similar and must therefore lead to similar numeric conclusions.

To assess the sampling stability of the anesthetic contrasts, we identified institutions that used both of a pair of anesthetics "frequently" (at least 10 percent of all operations and again at least 15 percent). We found a strong uniformity in the superiority of ether over halothane, nitrous oxide-barbiturate, and Other by this analysis, and strong evidence of lower death rates for nitrous oxide-barbiturate and halothane than for Other.

The last section of this chapter is devoted to a study of death-rate differences among institutions. Indirectly standardized mortality ratios based on age-risk-operation aggregation strata for the middle-death-rate operations vary in a 3.1-fold ratio over the 34 institutions. There is strong evidence that these differences are not due to sampling error. For a second way of looking at institutional variation, we chose six commonly used surgical procedures (involving about 15 percent of all the cases in the National Halothane Study) and studied institutional variation in death rates for them only. Again, we found large institutional variation; moreover, we found agreement between the list of institutions with high death rates for these chosen six operations and the list of high-death-rate institutions identified by the more comprehensive but less direct analysis using middle-death-rate operations. Further similar analyses using the four high-death-rate operations, separately and together, corroborated these results. We conclude that there are real and important differences in death rates among institutions, and we point to reasons for caution in interpreting these differences and raise questions calling for further study.

CHAPTER IV-6.
ANALYSIS FOR "PURE-AGGREGATION" STRATA

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The objective of stratification methods, as used in this study, is to bring together kinds of cases that are homogeneous with respect to death rate and then to compare the agents in such homogeneous classes for their standardized death rates. One way to make this stratification is to assemble the cells with the highest death rates in one stratum and then assemble the cells with the next highest death rates into the second stratum, etc. If the samples were sufficiently large, this stratification of observed death rates would agree (almost certainly) with the ideally correct stratification, which would be based on true cell death rates. But if the samples are quite small, the stratification based on the ordering of the cell death rates might be seriously in error.

In this chapter, we present the results of studies of death rates in terms of cell aggregation. There are, of course, as many possible ways of forming strata by cell aggregation as there are ways of defining cells. (Indeed, there are more, because there are many possible sweepup rules for any given cross-classification.) It is interesting that, if the many cells in a large cross-classification are coalesced into a single stratum, the "standardized rates" then will be merely the crude rates; if they are coalesced into two strata, high- and low-death-rate strata, we will have taken one step toward adjusting for the "interfering variables." In most of what follows, we have used 10 (sometimes 15) strata.

AGENT COMPARISONS BASED ON "PURE-AGGREGATION" STRATA

Aggregation of Cells Defined in the Smoothed Contingency-Table Analysis

In Chapter IV-3, we defined various ways of cross-classifying portions of the data into high-, middle-, and low-death-rate operations and cholecystectomies (summarized in Table 3 of that chapter). The pigeonholes corresponding to these classifications underlie the aggregations presented here. The observed values in the cells were summed over the categories of the variable agent, and rates computed from these sums were used for ordering and defining the aggregated strata. Once the strata were defined, the data were again broken down into the five agent categories so that standardized rates could be computed. Table 1 shows standardized death rates for various subsets of the data. These standardized death rates are based on 10 strata (except that occasionally it was possible to construct only nine), formed by collecting cells of the cross-classification in order of death rate and in such a way as to make the resulting strata approximately equinumerous in terms of deaths plus estimated exposed. In Table 1, we see patterns that are remarkably similar to those found in Table 1 of Chapter IV-5, which presented standardized death rates using strata obtained by fitting parameters to the same underlying pigeonhole system. Table 2 gives information similar to that in Table 1, but based on indirect standardization. This table is comparable with Table 2 of Chapter IV-5 and the figures are quite similar.

Results from the ORLA Cross-Classification

For each of the low-, middle-, and high-death-rate operation groups, it is possible to construct a system of cells indexed by age, length, risk, and operation, and then to aggregate cells into strata in order of their death rate. This leads to standardized death rates. In Table 3, the definitions of the classifications used are set forth; and in Table 4, the standardized death rates are exhibited, with the indirectly standardized mortality ratios. We see that for the low-death-rate operations the most notable features are the high death rates associated with cyclopropane and Other. In the middle-death-rate operations, cyclopropane and Other both have death rates of around 0.025, and the three remaining

TABLE 1.--DIRECTLY STANDARDIZED RATES BASED ON AGGREGATION OF CELLS USED IN SMOOTHED CONTINGENCY-TABLE ANALYSIS

Operation group	Agent					
	H	N-B	C	E	O	All
Low	0.0023	0.0016	0.0026	0.0018	0.0033	0.0022
Middle, model B	0.0195	0.0196	0.0277	0.0181	0.0255	0.0221
Middle, model A	0.0192	0.0195	0.0277	0.0184	0.0260	0.0221
High	0.0827	0.0931	0.1116	0.0819	0.1060	0.0933
Chole	0.0206	0.0266	0.0248	0.0255	0.0291	0.0238

TABLE 2.--STANDARD MORTALITY RATIOS BASED ON AGGREGATION OF CELLS USED IN SMOOTHED CONTINGENCY-TABLE ANALYSIS

Operation group	Agent				
	H	N-B	C	E	O
Low	1.07	0.73	1.19	0.81	1.45
Middle, model B	0.88	0.89	1.26	0.81	1.14
Middle, model A	0.87	0.88	1.26	0.82	1.17
High	0.89	1.00	1.20	0.85	1.12
Chole	0.86	1.08	1.01	1.03	1.10

TABLE 3.--DEFINITION OF VARIABLES USED IN ORLA PURE-AGGREGATION ANALYSES

	Age,* years	Length, min	Risk	Operation
Low	0-9	1 - 28	Unknown	1
	10-49	29 - 58	1, 2, 5	3
	50-69	59 - 118	3, 4, 6	55 60
	70 +	119 +	7	65 73 90
Middle	0-9	1 - 28	Unknown	5 groups of operations**
	10-39	29 - 58	1, 2, 5	
	40-49	59 - 118	3, 4, 6	
	50-59	119 - 238	7	
	60-69	239 - 388		
	70-79	389 +		
	80+			
High	0-9	1 - 28	Unknown	12
	10-49	29 - 58	1, 2, 5	33
	50-69	59 - 118	3, 4, 6	44
	70+	119+	7	48

*Cases with unknown age omitted.
**See Appendix 1 to Chapter IV-5.

anesthetic agents have death rates of around 0.020. In the high-death-rate operations, the comparisons among the agents are very much as in the middle-death-rate operations, except that nitrous oxide-barbiturate seems to lie between the two pairs, cyclopropane and Other, and ether and halothane.

Considerations Relating to Emergency Operations

Cyclopropane was used rather more heavily than halothane in emergency operations in all three death-rate groups. (This statement can be confirmed by looking at Tables EE-4, -5, and -6 of Chapter IV-2.) Because cyclopropane is used more extensively in the higher-risk categories, it is reasonable to inquire whether within any risk category the cyclopropane patients may not be "worse" than the halothane patients. That would happen if there were a general shift in the distribution of physical status of cyclopropane patients compared with halothane patients. If there were such a shift, it would bias the death-rate comparison, causing halothane to compare favorably with cyclopropane, partly because of this phenomenon. To check this possibility, a pure-aggregation analysis based on ORLA was done with all emergency-operation patients omitted completely; the corresponding standardized death rates are presented in Table 5. In that table, the rows labeled "Out" correspond to the analyses where emergency patients have been left out, and the rows labeled "In" correspond to analyses where they have been included. Obviously, the most striking feature of the data is the substantially lower death rate for every anesthetic agent that occurs when emergency operations are excluded. Looking at the bottom

TABLE 4.--DIRECTLY STANDARDIZED+ DEATH RATES BASED ON AGGREGATION OF CELLS IN AGE, LENGTH, RISK, AND OPERATION CROSS-CLASSIFICATION*

Operation group		Agent					
		H	N-B	C	E	O	All
Directly standardized death rate	High	0.0862	0.0920	0.1118	0.0908	0.1044	0.0934
	Middle	0.0200	0.0205	0.0261	0.0191	0.0249	0.0221
	Low	0.00217	0.00185	0.00302	0.00174	0.00304	0.00229
Indirectly standardized mortality ratio	High	0.918	0.994	1.15	0.873	1.09	1.00
	Middle	0.910	0.925	1.16	0.850	1.11	1.00
	Low	0.946	0.815	1.29	0.761	1.34	1.00

+ Standardizing population is "all agents."
* Aggregation (in order of D/(D+EE)) into 10 strata approximately equinumerous in terms of deaths-plus-randoms.

TABLE 5.--DEATH-RATE COMPARISONS BY ORLA AGGREGATION WITH AND WITHOUT EMERGENCY OPERATIONS
(Middle-death-rate operations only)

	Emergency operation	Agent					
		H	N-B	C	E	O	All
Directly standardized death rate	In	0.0200	0.0205	0.0261	0.0191	0.0249	0.0221
	Out	0.0157	0.0163	0.0209	0.0138	0.0192	0.0170
Mortality ratio	In	0.910	0.925	1.16	0.850	1.11	1.00
	Out	0.927	0.961	1.23	0.815	1.13	1.00

half of the table, where the directly standardized mortality ratios are exhibited, we see that there is no evidence of an effect of the sort described. The mortality ratio for cyclopropane is 1.16 when emergency patients are included and 1.23 when they are excluded. For halothane, there is also a difference, smaller but in the same direction. Generally, there are not large differences in the two patterns of mortality ratios.

Analysis Based on Aggregation of the Age-SLI Distribution for All Operations

Shock-likelihood index (SLI) is a numeric variable intended to represent the propensity for a given patient to experience shock on the operating table. The SLI score is determined from the operation code of the surgical procedure, and from the emergency status of the procedure (i.e., whether physical status was 1, 2, 3, or 4, rather than 5, 6, or 7). A detailed description of this index appears in Chapter IV-7. Shock includes six categories: unknown and five ordered classifications reflecting increasing probability of shock. The 7×6 two-way classification of shock and age was swept into 10 categories in order of death rates, so as to form categories as nearly equinumerous as possible in terms of deaths-plus-randoms. The directly standardized death rates were computed for each anesthetic agent, the standardizing population being the all-agents population. The directly standardized death rates obtained appear in Table 6, with corresponding mortality ratios. It is notable that the standardized death rate for halothane is almost exactly "average." As other analyses have repeatedly shown, cyclopropane and Other have higher than average death rates and nitrous oxide-barbiturate lower than average.

RELATION OF ANALYSES BASED ON REGRESSION STRATA AND PURE-AGGREGATION STRATA

We are able to compare the results arising from the two methods of strata formation in three different bodies of data. They are the contingency-table analysis data, the ORLA classification, and the age-shock (for all operations) data. The three sets of comparisons are not wholly similar.

In the case of the contingency-table analysis, the comparison amounts to comparing Tables 1 through 4 of Chapter IV-5 with Table 1 of this chapter. The similarity is striking, and there are no important differences.

In the case of the ORLA studies, the high-, middle-, and low-death-rate operation groups'

TABLE 6.--DEATH-RATE COMPARISONS BASED ON SHOCK*-AGE AGGREGATION STRATA
(10 strata swept on D+R)

Directly standardized	Agent					
	H	N-B	C	E	O	All
Death rate	0.0195	0.0169	0.0216	0.0156	0.0237	0.0194
Mortality ratio	1.00	0.861	1.11	0.804	1.22	

*All operations; unknown shock included.

TABLE 7.--DIRECTLY STANDARDIZED DEATH RATES BASED ON CELL AGGREGATION OF ORLA CROSS-CLASSIFICATION
(Middle-death-rate operations)

Category sweepup		Agent					
		H	N-B	C	E	O	All
10	Deaths	0.0208	0.0204	0.0256	0.0196	0.0249	0.0221
	EE	0.0195	0.0194	0.0273	0.0180	0.0262	0.0221
	D+R	0.0200	0.0205	0.0261	0.0191	0.0249	0.0221

TABLE 8.--DIRECTLY STANDARDIZED DEATH RATES BASED ON ORLA LOGIT REGRESSION STRATA
(Middle-death-rate operations)

Category sweepup		Agent					
		H	N-B	C	E	O	All
10	Deaths	0.0205	0.0199	0.0270	0.0177	0.0254	0.0221
	EE	0.0198	0.0189	0.0282	0.0169	0.0263	0.0221
	D+R	0.0204	0.0194	0.0275	0.0173	0.0256	0.0221
15	Deaths	0.0208	0.0202	0.0270	0.0179	0.0256	0.0221
	EE	0.0201	0.0193	0.0278	0.0166	0.0260	0.0221
	D+R	0.0205	0.0196	0.0274	0.0173	0.0256	0.0221

standardized death rates obtained by regression-based strata appear in Table 5 of Chapter IV-5, and those obtained by aggregation appear in Table 4 of this chapter. The agreement is strong, but less than with the contingency-table analysis. For the low-death-rate operations, the death rates are in close agreement, the only notable difference being a larger cyclopropane death rate in the aggregation-based rates; it is not clear that the difference has meaning, occurring in the fourth decimal place. For the middle-death-rate operations, the death-rate comparisons among anesthetics are qualitatively alike; generally, the differences among the agents are greater in the regression-strata figures. For the high-death-rate operations, the pictures are again qualitatively alike, with the contrasts among agents being generally less great in the aggregation-strata figures.

Further comparison of the two modes of analysis for the middle-death-rate operations is made in Tables 7 and 8. The former shows the standardized death rates for sweepup (with 10 categories by aggregation) by deaths, estimated exposed, and deaths-plus-randoms. The latter shows the standardized death rates for sweepup (into 10 and 15 categories by regression) by deaths, estimated exposed, and deaths-plus-randoms. The generally more pronounced differences for regression strata appear throughout.

If we turn to the age-shock data, which cover the full range of operations, the similarity of results for regression and aggregation is again striking. Table 9 presents directly standardized mortality ratios for the shock-age data where the stratification has been done by regression and by aggregation. There are no notable disagreements. To understand the reasons for the similarity, we took one body of data, the middle-death-rate ORLA classification, and inquired into the correspondence between the strata arrived at by the stratification schemes. Every pigeonhole can be characterized by a pair of numbers: its regression stratum and its aggregation stratum. In Table 10, we exhibit all the deaths in the middle-death-rate operations in a two-way classification. The row represents the aggregation stratum in

TABLE 9.--DIRECTLY STANDARDIZED MORTALITY RATIOS FOR THE SHOCK-AGE DATA, STRATIFIED BY REGRESSION AND BY PURE AGGREGATION
(All operations)

Mode of stratification	Agent				
	H	N-B	C	E	O
Regression*	1.00	0.892	1.13	0.788	1.29
Aggregation+	1.00	0.861	1.11	0.804	1.22

*Source, Table 7, Chapter IV-5. +Source, Table 6, this chapter.

TABLE 10.--DISTRIBUTION OF DEATHS IN TWO-WAY CLASSIFICATION* OF REGRESSION AND AGGREGATION STRATA FOR MIDDLE-DEATH-RATE OPERATIONS

Ordered "aggregation strata"	Ordered "regression strata"									
	1	2	3	4	5	6	7	8	9	10
1	774	139	33	16	0	0	0	0	0	0
2	163	510	170	60	30	13	0	0	0	0
3	16	236	373	168	130	2	4	31	0	0
4	0	17	214	232	175	180	66	56	22	2
5	1	2	121	271	259	184	49	17	0	13
6	0	36	104	133	206	267	119	71	16	0
7	0	0	0	0	24	115	155	429	259	19
8	0	1	0	22	81	165	346	158	103	27
9	0	4	0	11	3	2	104	119	401	232
10	0	0	0	0	2	9	52	59	86	413

r= 0.88

*Both sets formed by sweeping to 10 strata approximately equinumerous in terms of deaths.

TABLE 11.--CORRELATION COEFFICIENTS FOR REGRESSION- AND AGGREGATION-STRATUM IDENTIFICATION OF "CASES" FOR SIX SWEEPUP RULES

Number of strata	Swept by counting:		
	Deaths	Estimated exposed	Death + randoms
10	0.88	0.92	0.95
15	0.88	0.94	0.96

which the death belongs, and the column represents the regression stratum in which the death belongs. (The strata have been swept up in terms of deaths.) It is clear that there is a strong similarity between the two systems of strata. The correlation coefficient between two indices is 0.88. Six such two-way tables were prepared, corresponding to the six modes of sweepup (10 or 15 categories in terms of deaths, or estimated exposed, or deaths-plus-randoms). The correlation coefficients for these six tables are shown in Table 11. All are at least 0.88; if sweeping is in terms of deaths-plus-randoms, the similarity of strata is greatest. These considerations lead to the conclusion that, for any given scheme of cross-classification, the similarity of agent comparisons based on aggregation strata and those based on regression strata is largely to be expected, because the strata developed by the two methods are quite similar.

VARIATION AMONG INSTITUTIONS OF THE COMPARISONS BETWEEN ANESTHETICS (IN TERMS OF STANDARDIZED DEATH RATES USING AGGREGATION STRATA)

In this section, we shall study the agent comparisons within separate institutions, rather than lumping the entire body of data across institutions. There are two reasons for examining the agent comparisons in this way: (1) to prevent hospital effects from distorting agent comparisons, and (2) to assess the sampling stability of over-all figures. Each of these reasons deserves elaboration.

Chapter IV-2 showed that different institutions had very different death rates and patterns of use of the various anesthetic agents. Comparisons of the agents that simply lump the hospitals together are subject to the risk that the apparent agent differences are partly created by (or partly

TABLE 12.--INDIRECTLY STANDARDIZED MORTALITY RATIOS (BASED ON AGE, RISK, AND OPERATION AGGREGATION STRATA) DISPLAYED FOR 34 INSTITUTIONS BY AGENT
(Middle-death-rate operations only)

Inst.	Agent					
	H	N-B	C	E	O	All
1	0.8247	0.4240	92.2436	0.9324	0.7800	0.7286
2	1.2986	1.1399	1.3854	1.9593	1.3726	1.3221
3	0.9142	0.7468	1.0164	0.2500	1.0913	0.8619
4	0.8955	1.0532	1.2038	1.8531	1.0961	1.1324
5	1.2435	1.8274	1.5046	4.6516	1.7303	1.5633
6	0.7483	0.9648	0.5769	1.2044	0.9996	0.8952
7	1.3859	1.1852	1.0960	3.5477	2.3088	1.5979
8	0.6419	0.9000	2.9322	0.6582	0.6365	0.6834
9	1.5906	0.8457	0.8529	0.5005	0.6220	0.7582
10	1.1002	1.0472	1.4540	1.6927	1.6482	1.2738
11	0.5594	1.0859	0.6282	0.5129	1.2663	0.7121
12	1.0749	0.6537	1.2314	10.7208	1.3447	1.1641
13	1.7270	1.3716	2.6247	0.6957	0.8985	1.4877
*14	0.3766	0.6437	0.8852	0.2675	0.5233	0.5771
15	1.7181	0.8131	1.1431	0.7303	1.1303	1.0351
16	1.8225	1.2879	1.2910	4.9441	1.2829	1.3380
*17	0.9637	0.5095	0.4845	0.4168	1.2740	0.8583
18	0.6505	1.0058	0.9306	0.2787	1.2133	0.8384
19	1.3888	0.4618	1.2644	6.3394	2.4099	1.0609
20	1.0993	0.4693	1.2409	0.9873	1.0775	1.0213
21	0.7453	0.7394	0.7899	3.2776	0.7377	0.7695
22	0.9032	1.1259	1.0228	0.6107	2.5697	1.1257
*23	0.3817	0.6082	0.6334	-1.0000	0.9434	0.5741
24	1.4478	0.9614	2.0318	7.5223	2.9339	1.4329
25	1.0838	1.1944	1.3809	3.5390	1.5384	1.3756
26	0.8517	0.6435	6.3498	0.9698	0.9033	0.9426
27	0.6575	1.3785	1.0248	1.3128	1.0225	0.9400
*28	0.7392	0.6491	0.1345	2.1928	0.6445	0.7056
*29	0.7674	1.6757	1.1747	0.2500	0.6343	0.8416
30	0.7453	0.5345	1.4036	-1.0000	0.8566	0.7379
*31	1.6282	1.6556	1.5655	7.0894	9.5743	1.7667
32	0.6228	0.5942	1.0281	0.2500	0.9031	0.7576
33	0.6148	0.9210	0.8387	1.1509	0.8609	0.7928
*34	0.8377	3.7092	2.2157	1.1811	0.8835	1.2088
All	0.899	0.907	1.212	0.803	1.140	1.000

*Starred institutions had fewer than 200 deaths in entire Study. -1.0000 denotes that there were no estimated exposed or deaths associated with the cell.

TABLE 13.--DISTRIBUTION OF RANK WITHIN INSTITUTION FOR FIVE ANESTHETICS IN 32 INSTITUTIONS--RANKS APPLIED TO MORTALITY RATIOS* INDIRECTLY STANDARDIZED FOR AGE, OPERATION, AND PHYSICAL STATUS USING 15 AGGREGATION STRATA
(Middle-death-rate operations)

Rank*	Agent					
	H	N-B	C	E	O	Average
1	6	8	4	11	3	6.4
2	12	8	4	1	7	6.4
3	7	6	9	2	8	6.4
4	5	7	8	4	8	6.4
5	2	3	7	14	6	6.4
Rank sum	81	85	106	105	103	96

$\chi^2_4 = 7.325$ $\quad p = 0.122$

*Rank 1 given to the smallest mortality ratio, 5 to the largest.

masked by) the joint effect of these two factors concerning institutions. For example, one of the agents, say A, might tend to be used largely in hospitals with difficult patient loads and thus high death rates, whereas another agent, say B, might be used largely in hospitals with few difficult cases and thus low death rates. This combination of circumstances would lead to the spurious appearance of A's having a higher death rate than B. In some measure, this kind of difficulty is avoided by standardizing for age, operation, and risk, but if we not only make adjustments, but then look directly at the agent comparisons within the various hospitals, we need not rely wholly on the efficacy of adjustments. Furthermore, the designation of the physical status of a patient may vary from one hospital to another, and perhaps to some extent the designation of the operation code may, also (consider, for example, the judgment factor in deciding whether a mastectomy is or is not "radical"). Such hospital variations would partially offset the corrective effects of adjustments through standardization. But these idiosyncrasies will tend to remain constant for all agents within a given hospital, and not distort comparisons there.

We would like to attach some measure of firmness to the statistical contrasts between the agents (differences between death rates associated with the anesthetics). If a contrast is small but consistent from one hospital to another, we may have high confidence that it reflects a difference between the anesthetics, and not merely a fortuitous averaging of conflicting comparisons that happened not to cancel out wholly in our particular sample of 34 institutions. Similarly, a contrast between agents, even if large, may not be trustworthy if it is the average of large swings in both directions. To resolve these matters, it is necessary to see how these agents compare, hospital by hospital.

It would certainly be attractive to compare the agents within hospitals over all operations, but we have elected not to. Thirty-eight percent of the deaths arose from the four high-death-rate operations. These had sharply varying patterns of anesthetic use; for example, cyclopropane and ether were rarely used in operation 12, and ether was never used in operation 33. The statistical effects of such great differences in usage are difficult to appraise, and we have chosen to exclude the four high-death-rate operations for individual study. Because only 5 percent of the deaths arose from the low-death-rate operations, we have also excluded them. Thus, we focus our attention on agent comparisons within hospitals for the middle-death-rate operations.

We have used indirect standardization based on 15 strata (equinumerous in terms of deaths-plus-randoms), obtained by aggregating cells from the age, operation, and physical status cross-classification; these three variables have been categorized as in Chapter IV-5. Table 12 shows the indirectly standardized mortality ratios obtained in the 34 institutions for the middle-death-rate operations. The seven institutions having fewer than 200 deaths in all have been starred. The last row of this table displays the indirect standardized mortality ratios for the five anesthetics where cases in all institutions have been accumulated. There ether has the lowest ratio, 0.803; halothane and nitrous oxide-barbiturate have essentially equal ratios, 0.9; and Other and cyclopropane have the highest ratios, 1.14 and 1.21, respectively.

An assessment of the degree to which the over-all results reflect consistent intrahospital differences can be approached by the following procedure: For each institution, replace the five figures for the agents by their ranks, assigning 5 to the highest and 1 to the lowest; omitting institutions 23 and 30, in which no ether was used, sum the ranks for each agent. If such a rank sum is large, it means that in many institutions the death rate for that agent was high; if the rank sum is small, it means that in many institutions the death rate for that agent was small. The rank sums obtained by this method are displayed in Table 13. These sums form the basis for a test of significance called Friedman's rank analysis of variance; application of that test yields a chi-square with four degrees of freedom equal to 7.325, which corresponds to a significance level of 0.122.

This result is a very weak indication of consistent differences among the anesthetic agents. But the distribution of ranks in the ether column in Table 13 strikes the eye. In more than three-fourths of the hospitals, it was either best or worst; in Chapter IV-2, we learned that it had a very spotty usage pattern, being scarcely used in some hospitals and widely used in others. These are good reasons to omit ether from our present consideration. Furthermore, the presence of ether has absorbed more than one-third of the extreme ranks (i.e., ranks 1 and 5) in the entire table, restricting the opportunity of other agent differences to become manifest. Therefore, in Table 14 we exhibit results of the rank analysis of variance with ether omitted, and with institutions 23 and 30 present (because their nonuse of ether is no longer a reason for their exclusion). The value of chi-square is now 10.2, which for three degrees of freedom has a significance level of 0.017 and is probably a reliable indication of real differences among these four agents. This conclusion has some vagueness, in that it fails to answer such more precise and interesting questions as: "Which agents are associated reliably with lower death rates than which others?" Instead, it simply gives us the shotgun answer: "There are some real differences." Another shortcoming of the over-all rank analysis of variance just applied is that it treats the institutions with complete symmetry and the agents with complete symmetry. Thus, important distinctions may be ignored, e.g., whether an institution was large or small, or whether some

TABLE 14.--DISTRIBUTION OF RANK WITHIN INSTITUTION FOR FOUR ANESTHETICS (ETHER OMITTED) IN 34 INSTITUTIONS--RANKS APPLIED TO MORTALITY RATIOS* INDIRECTLY STANDARDIZED FOR AGE, OPERATION, AND PHYSICAL STATUS USING 15 AGGREGATION STRATA
(Middle-death-rate operations)

Rank*	H	N-B	C	O	Average
1	11	12	5	6	8.5
2	12	9	6	7	8.5
3	7	8	12	7	8.5
4	4	5	11	14	8.5
Rank sum	72	74	97	97	85

$\chi^2_3 = 10.2$ P= 0.017

*Rank 1 given to the smallest mortality ratio, 4 to the largest.

TABLE 15.--PAIRWISE ANESTHETIC COMPARISONS* FOR MIDDLE-DEATH-RATE OPERATIONS IN INSTITUTIONS IN WHICH BOTH AGENTS IN PAIR WERE USED IN AT LEAST 10% OR 15% OF ALL PROCEDURES**

10%	N-B	C	E	O
H	17/29	4/22	5/10	7/23
N-B		7/19	6/11	7/20
C			4/6	11/18
E				1/6

15%	N-B	C	E	O
H	9/20	3/14	3/4	4/13
N-B		4/12	4/4	6/10
C			1/1	7/9
E				0/2

*Comparisons based on age-operation-physical status indirectly standardized mortality ratios.
**Entries are shown as fractions. The denominator is the number of institutions having 10 (or 15) percent dual use; the numerator is the number of institutions in which LSMR for the row anesthetic exceeded that for the column anesthetic. Thus, the second entry in the first row of the upper table shows that in four of 22 institutions halothane had a higher ratio than cyclopropane and in 18 cyclopropane had a higher ratio than halothane.

agent was scarcely used at all in a particular institution. So it would be good to look at these agent contrasts within institution after multiple adjustments, for a second time.

Table 15 offers such a second look. From Table EE-22 of Chapter IV-2, we can identify the institutions in which any agent was used "frequently," however we may choose to define that word. We have used two definitions: (1) we have taken an anesthetic agent to be used "frequently" in an institution if at least 10 percent of all the surgical procedures in that institution involved that agent; and (2) we have used 15 percent in a similar way. From Table EE-22, we can now identify for each pair of anesthetic agents the institutions in which both members of the pair were used frequently (10 or 15 percent). In Table 15, the results appear. This table has two parts: the upper panel relates to institutions in which there was dual usage of at least 10 percent, and the lower panel to institutions in which there was dual usage of at least 15 percent. Each entry is in the form of a fraction; the denominator shows how many institutions satisfy the usage requirement, and the numerator shows in how many of those the anesthetic for the row had a higher mortality ratio than did the anesthetic for the column. Thus, the second entry in the first row of the upper panel shows that in four of 22 institutions halothane had a higher ratio than cyclopropane; in the remaining 18, cyclopropane had a higher ratio than halothane. The table reinforces no strong conclusions, except for a superiority of halothane over cyclopropane (the significance level in the upper panel is 0.005, and in the lower panel is 0.06).*

We can also see that the data are consistent with a possible lower rate for halothane in comparison with Other, and of nitrous oxide-barbiturate in comparison with cyclopropane, although neither of these contrasts is statistically significant. Finally, it is worth observing that ether, on which there is the least information, provides no strong indication of difference from any of the other agents.

*The halothane-cyclopropane comparison just described was looked at in a similar way by F. Mosteller. He defined frequent usage in terms of 10 percent dual usage in the middle-death-rate operations (rather than all operations); in place of weighting the deaths and death rates in the various strata by indirect standardization, he has coarsely accumulated the cases in the strata, beginning with the strata with the highest rates, the "top" strata. The findings are, naturally, very similar. Mosteller's report follows:

To get still another look at halothane and cyclopropane for the middle-death-rate operations, institution by institution, I considered institutions using each of these two anesthetics in at least 10 percent of the middle-death-rate operations. Starting at the category with the highest death rate, I counted down until both anesthetics had at least 50 deaths in the institution. (This meant omitting some institutions that had fewer than 50 deaths.) Then death rates were compared. If possible, another 50 deaths were considered, and so on. For details, see the table (on the next page). Finally, there was a residual category. In 11 institutions such a comparison could be made. Halothane had the lower rate in 10 of the 11 top categories. Halothane had the lower rate in both of the second categories, and cyclopropane the lower in the single third category. In the residual categories, halothane had the lower rate in seven of 11 comparisons. In the residual categories the differences are usually tiny, for these are low-death-rate categories. This is a summary of the comparisons:

	Lower death rate	
	H	C
Top categories	10	1
Second categories	2	0
Third category	0	1
Residual categories	7	4

DEATH-RATE ANALYSIS SUMMARIZED IN FOOTNOTE:
COMPARISONS, BASED ON ORA STRATA, OF HALOTHANE AND CYCLOPROPANE
FOR FREQUENTLY USING INSTITUTIONS FOR MIDDLE-DEATH-RATE OPERATIONS

Institution	Category	Halothane			Cyclopropane			
		D	EE	D/EE	D	EE	D/EE	Lower
2	Top	54	100	54.0	78	131	59.5	H
	2nd	89	847	10.5	52	415	12.5	H
	Res.	18	1508	1.2	3	439	0.7	C
5	Top	63	190	33.2	61	136	44.9	H
	2nd	51	436	11.7	72	436	16.5	H
	3rd	54	953	5.7	60	1415	4.2	C
	Res.	21	2476	0.8	26	5771	0.5	C
7	Top	53	407	13.0	56	271	20.7	H
	Res.	25	1377	1.8	8	1378	0.6	C
10	Top	64	584	11.0	141	609	23.2	H
	Res.	71	5944	1.2	39	1950	2.0	H
12	Top	53	524	10.1	80	733	10.9	H
	Res.	46	4354	1.1	30	3244	0.9	C
21	Top	68	629	10.8	70	456	15.4	H
	Res.	61	10734	0.6	41	4513	0.9	H
22	Top	82	338	24.3	52	312	16.7	C
	Res.	71	7983	0.9	37	3198	1.2	H
24	Top	61	282	21.6	88	205	42.9	H
	Res.	22	1286	1.7	21	258	8.1	H
25	Top	59	349	16.9	82	350	23.4	H
	Res.	26	1366	1.9	24	653	3.7	H
26	Top	67	965	6.9	50	96	52.1	H
	Res.	16	8981	0.2	4	901	0.4	H
33	Top	66	768	8.6	60	467	12.8	H
	Res.	44	3235	1.4	16	851	1.9	H

The foregoing analysis has the strong point that it compares agents only in hospitals in which they were much used. At the same time, it ignores a considerable portion of the data. We now turn to two approaches that utilize all the information more fully. One takes special account of the reliability of the agent contrasts, and the other takes special account of the size of those contrasts. We compare the results for the various agents in the 34 hospitals shown in Table 12. Both approaches use a statistic of the form shown below:

$$T_{\alpha\beta} = \sum_{i=1}^{34} r_i(\alpha,\beta)\ \mathrm{sgn}(X_{\alpha i} - X_{\beta i}).$$

This expression is the sum of 34 terms, one for each hospital. The expression, $\mathrm{sgn}(X_{\alpha i} - X_{\beta i})$, denotes the sign of the difference between the logarithms of the indirectly standardized mortality ratios for the two agents, α and β. The expression, $r_i(\alpha,\beta)$, represents the "rank" in institution i for the agent pair α,β. This rank is an integer from 1 to 34, assigned as described below.

For the first approach, rank 1 is assigned to the institution for which the variance of the difference between the logarithms is greatest, and rank 34 to the institution for which it is least. This method of analysis provides a statistic that gives the greatest weight to the differences that are best determined, in the sense of having small variance. The distribution of the statistic, under the hypothesis of no agent differences, is the same as the null distribution of Wilcoxon's signed rank test. There are a few institutions for which the logarithm of the indirectly standardized mortality ratio is undefined, either because there were no deaths, or because there were no estimated exposed, or both. In such cases, the range of the sum and the range of the ranks are reduced to the number of institutions for which the differences are defined. The bottom panel of Table 16 shows how many institutions were involved in the various agent comparisons. The top panel of that table shows the value of the statistic $T_{\alpha\beta}$ divided by its null standard error. These numbers are referable to tables of the normal distribution for the assessment of statistical significance. A positive number means that the indirectly standardized mortality ratio for the agent shown in the row was greater than that for the agent shown in the column. Values exceeding 1.96, the two-sided 5 percent point of the normal distribution, are starred.

The second approach leads to the second panel of Table 16. The approach is wholly analogous to the first, except that the ranks have been assigned, not in terms of precision of the contrasts, but in terms of their magnitudes; in particular, the quantities

$$|\log \mathrm{ISMR}_\alpha - \log \mathrm{ISMR}_\beta|_i \qquad (i = 1, \ldots, 34)$$

were ranked, with the largest rank being assigned to the greatest such quantity. This method of analysis gives greatest weight to the greatest differences in logarithms, which means the greatest ratio of indirectly standardized mortality ratios.

Study of Table 16 shows, in both panels, lower rates for halothane than for cyclopropane, and lower rates for halothane than for Other. Ether, in the lower panel, gives indication of having higher rates than either halothane or nitrous oxide-barbiturate, but the corresponding indications in the upper panel are weak, and we cannot conclude that the comparisons are to be trusted. The remaining strong indications in the table are the comparisons of nitrous oxide-barbiturate with cyclopropane and with Other. In the lower panel, both of these are large, and in the upper panel, rather strongly corroborative. In an effort to settle these two comparisons, a more powerful analysis was used, which takes account of both the variability and the size of an agent

TABLE 16.--ANESTHETIC COMPARISONS (MIDDLE-DEATH-RATE OPERATIONS) AFTER INDIRECT STANDARDIZATION (FOR AGE, OPERATION, AND PHYSICAL STATUS) OBTAINED BY APPLYING SIGNED RANK TESTS TO DATA OF TABLE 12[1]

Ranks based on variability of contrast[2]

	N-B	C	E	O
H	1.05	-3.10*	-1.31	-2.40*
N-B		-1.74	-0.98	-1.72
C			-0.27	0.35
E				1.01

Ranks based on size of contrast[3]

	N-B	C	E	O
H	0.28	-2.85*	-2.39*	-2.83*
N-B		-2.21*	-2.07*	-2.42*
C			-0.48	-0.04
E				1.26

Number of institutions entering into comparison

	N-B	C	E	O
H	34	33	29	34
N-B		33	29	34
C			28	33
E				29

[1] A positive number means that the agent shown in the row had a higher ISMR than the agent shown in the column; thus the first entry in the second row of the upper table, -1.74, means that the ISMR for nitrous oxide-barbiturate was lower than that for cyclopropane, and the significance of the difference can be ascertained by referring 1.74 to a normal table.

[2] "Variability" means variance of (log $ISMR_\alpha$ - log $ISMR_\beta$), where α and β denote the agent pair. Largest rank given to smallest variance.

[3] "Size of contrast" means $|\log ISMR_\alpha - \log ISMR_\beta|$. Largest rank given to largest such absolute difference.

contrast within a hospital. The methods are explained in Appendix 3. The results are that the nitrous oxide-barbiturate--cyclopropane comparison yields a normal deviate of -2.75, and the nitrous oxide-barbiturate--Other comparison one of -2.86. Both are highly significant.

In the following section, there is an account of how six frequent operations came to be studied in all 34 hospitals. These six operations had death rates ranging from about one-fourth of 1 percent to about 5 percent. Standardizing for the number of exposures to the six operations enables the construction of logarithms of the indirectly standardized mortality ratios for each agent in each hospital. (These data are not displayed.) The numbers of defined agent contrasts for these six operations are displayed in the bottom panel of Table 17. The upper two panels again show the values of the signed rank statistics divided by their null standard errors, and can be interpreted as before. The starred values indicate reliably lower death rates associated with halothane in comparison with both cyclopropane and Other, and with nitrous oxide-barbiturate in comparison with Other. In addition, there is some suggestion that halothane has a lower death rate than nitrous oxide-barbiturate for these six operations.

The two analyses corresponding to Tables 16 and 17 are not statistically independent. Table 16 is based on all middle-death-rate operations after standardization on age-operation-physical status aggregation. It is thus a rather highly derived and heavily adjusted set of statistics that affords the base. The figures in Table 17 have been subjected to no adjustment whatever (other than standardization for frequency for these six

TABLE 17.--AGENT COMPARISONS[1] (FOR SIX SELECTED OPERATIONS[2]) OBTAINED BY APPLYING SIGNED RANK TESTS TO STANDARDIZED MORTALITY RATIOS ANALOGOUS TO P* IN TABLE 24

Ranks based on variability of contrast[3]

	N-B	C	E	O
H	-1.80	-1.98*	-0.86	-3.40*
N-B		-1.79	0.26	-2.07*
C			1.29	-0.09
E				-1.83

Ranks based on size of contrast[4]

	N-B	C	E	O
H	-1.98*	-2.98*	-1.08	-3.81*
N-B		-1.63	-0.31	-2.58*
C			1.45	-0.01
E				-1.68

Number of institutions entering into comparison

	N-B	C	E	O
H	28	31	20	32
N-B		25	17	26
C			19	30
E				20

[1] A positive number means that the agent for the row had a higher ISMR than the agent for the column.

[2] The description of these six operations and the direct standardization are explained later in this chapter.

[3] "Variability" means variance of (log $ISMR_\alpha$ - log $ISMR_\beta$), where α and β denote the agent pair. Largest rank given to smallest variance.

[4] "Size of contrast" means $|\log ISMR_\alpha - \log ISMR_\beta|$. Largest rank given to largest such absolute difference.

TABLE 18.--PAIRWISE ANESTHETIC COMPARISONS* FOR FOUR HIGH-DEATH-RATE OPERATIONS IN INSTITUTIONS IN WHICH BOTH AGENTS IN PAIR WERE USED IN AT LEAST 10% OR 15% OF ALL PROCEDURES**

		10%					15%			
		N-B	C	E	O		N-B	C	E	O
Operation 12	H	13/18	1/1	3/4	10/15	H	9/11	0/0	3/4	6/9
	N-B		0/0	2/3	4/10	N-B		0/0	2/3	2/4
	C			0/1	0/2	C			0/0	0/1
	E				0/2	E				0/1
Operation 33	H	4/12	2/7	0/0	4/10	H	2/7	1/4	0/0	2/5
	N-B		3/5	0/0	5/6	N-B		2/3	0/0	3/4
	C			0/0	3/5	C			0/0	0/0
	E				0/0	E				0/0
Operation 44	H	8/22	6/19	6/9	9/19	H	7/14	4/13	2/4	5/12
	N-B		5/13	6/7	4/13	N-B		5/9	2/3	2/6
	C			4/5	8/16	C			1/1	5/9
	E				3/5	E				1/2
Operation 48	H	12/21	3/18	4/6	7/17	H	8/13	3/13	1/3	4/6
	N-B		4/14	1/7	8/14	N-B		2/7	1/2	2/5
	C			2/5	7/16	C			1/1	4/9
	E				2/4	E				2/2

*Comparisons based on age-physical status indirectly standardized mortality ratios.
**Entries are shown as fractions. See footnote 2 to Table 15.

operations) and are very directly interpretable, although liable to distortions from imbalances in risk and age; the data represent about one-sixth of all the cases in the Study. There is a reasonable concordance between the conclusions from the two analyses.

Let us summarize our findings for the three types of analysis we have reported:

(1) that halothane was associated with lower death rates than cyclopropane is separately demonstrated in the case of the frequent-usage analyses, in the case of the signed rank tests on indirectly standardized rates for the middle-death-rate operations, and on the panel of six selected operations;

(2) that halothane was associated with lower rates than Other is separately demonstrated in the case of the signed rank analyses and on the panel of six operations; the frequent-usage analysis is consistent with this, but only weakly confirmatory;

(3) that nitrous oxide-barbiturate was associated with lower rates than cyclopropane is separately demonstrated by the signed rank tests (after supplementary analysis) on middle-death-rate operations after adjustment, and weakly confirmed both by the frequent-usage analysis and on the panel of six operations; and

(4) that nitrous oxide-barbiturate was associated with lower rates than Other is separately demonstrated by the signed rank tests (after supplementary analysis) and on the panel of six operations; there is no confirmation of this finding from the frequent-usage analysis, although there is no incompatibility either.

The above conclusions lead us, with considerable confidence, to regard halothane as having had lower rates than cyclopropane and lower rates than Other and, with only slightly less confidence, to regard nitrous oxide-barbiturate as having had lower rates than cyclopropane and lower rates than Other.

The only "positive" indications not summarized in the above statement are suggestions that ether may have had higher rates than either halothane or nitrous oxide-barbiturate* in the middle-death-rate operations after adjustment for age, operation, and physical status. We note these indications, but are unprepared to assert

*Reference to Appendix 3 shows that the analysis of that section (which affirms the halothane-cyclopropane, halothane-Other, nitrous oxide-barbiturate--cyclopropane, and nitrous oxide-barbiturate--Other contrasts) yields the following contrasts:

$$\log\left(\frac{ISMR_H}{ISMR_E}\right) = -0.319 \text{ with s.e. } 0.167$$

$$z = \frac{-0.319}{0.167} = -1.91$$

$$\log\left(\frac{ISMR_{NB}}{ISMR_E}\right) = -0.380 \text{ with s.e. } 0.177$$

$$z = \frac{-0.380}{0.177} = -2.15$$

confidence in them, inasmuch as the pattern of usage of ether is both sparse and erratic.

In concluding this section, we take a glimpse at the results for the four high-death-rate operations. The findings are essentially negative, but the data are shown in order to complete the record. Table 18 is constructed in the same way as Table 15. It shows for each of the high-death-rate operations the number of institutions with 10 and 15 percent dual usage, with the number of institutions in which each agent had a mortality ratio exceeding that of each other agent. The most striking feature of this table is the paucity of large denominators; this shows the rarity of institutions whose experience with these operations was sufficiently extensive to permit computing indirectly standardized mortality ratios for both anesthetics. In the entire table, only one indication appears strong, the halothane-cyclopropane contrast in operation 48 (large bowel). Because there have been so many opportunities to "find something," i.e., so many comparisons to examine, we refrain from taking this result as conclusive, but it poses the interesting question of whether halothane is actually superior to cyclopropane for this operation. Table 19 summarizes the results for operations 12, 33, 44, and 48 in the same way that Table 16 does for the middle-death-rate operations. In the entire table, three comparisons exceed 2: halothane--nitrous oxide-barbiturate for operation 12, and halothane-cyclopropane and cyclopropane-ether for operation 44, where ranks are assigned by the magnitudes of the differences of the logarithms of the indirectly standardized mortality ratios. Each gets some corroboration from the other signed rank analysis.

COMPARISON OF INSTITUTIONAL DEATH RATES AFTER STANDARDIZATION BY AGE-RISK-OPERATION AGGREGATION AND AFTER DIRECT COMPARISON FOR SIX SELECTED COMMON SURGICAL PROCEDURES

Variation of death rates among institutions before and after standardization (for one variable at a time) was discussed in Chapter IV-2. The observed death rate among institutions varied from a low of 0.00268 to a high of 0.06405. The ratio of these extremes is about 1:25. Standardization for operation did the most to equalize the indirectly standardized mortality ratios. The effect of standardization by that variable was to reduce the ratio of largest to smallest indirect mortality ratios from about 25:1 to about 9:1.

In this section, we discuss the death-rate experience in the various institutions after standardization for several variables simultaneously, reaching over various groups of operations, to a total of seven analyses. We have applied cell aggregation to the cross-classification of age, risk (physical status), and operation as those variables are defined in Appendix 1 to Chapter IV-5. The seven analyses are based on the middle-death-rate operations (five classes), the high-death-rate operations (four classes), the middle- and high-death-rate operations (nine classes), and the four high-death-rate operations taken separately (with operation disappearing as a classification variable). In the seven analyses, age and risk always are used with seven and four classes, respectively. The cross-classification, whatever it was, was swept in death-rate order into 15 categories equinumerous in terms of deaths-plus-randoms. These strata were then used for the construction of indirectly standardized mortality ratios for each agent within each hospital (the reference population being "all agents" in the particular hospital). Table 12 displays these standardized mortality ratios for the middle-death-rate operations. Interest attaches to two kinds of features in that table. From the first five columns it is possible to make a detailed study, institution by institution, of differences in death rates by anesthetics, and so to assess their sampling reliability. This investigation was done in the preceding section. The second kind of investigation is the study of the institutional rates themselves (as opposed to the comparisons among anesthetics)--the topic of this section.

The largest mortality ratio in Table 12 is 1.77 for institution 31, and the smallest is 0.574 for institution 23. The ratio of these two numbers is about 3.1.* The interpretation of these figures is that, after we have taken account of the variables operation, physical status, and age, there remains for the middle-death-rate operations a three-fold variation in institutional death rates for which no further explanation is at hand, and for which explanation would be desirable. It is notable that this institutional variation is definitely smaller than was obtained by adjustment for any single variable.** This is partly because only the middle-death-rate operations are involved here, whereas standardization in Chapter IV-2 was applied to the data for all operations, and partly because the efficacy of multiple adjustment is involved. In the following analyses, we have not adjusted for anesthetics, because the order of magnitude of their differences is very much smaller than the observed differences between institutions.

*Because some of the institutions are much smaller than others, it is wise to inquire how strongly indications referring to the entire set of institutions may depend on possible peculiarities of the smallest institutions. A way to do this is to look at institutional variation ignoring the smallest institutions. For this reason we have starred, in Table 12, all those (seven) with fewer than 200 deaths. For the unstarred institutions, the extreme mortality ratios are 1.60 and 0.683, which still differ by a factor of 2.3. So we conclude that the variation is not an artifact of small-institution fluctuation.

**If the seven small institutions are omitted, it is still true that standardization for no single variable reduces the institutional variability as substantially as does the multiple adjustment.

TABLE 19.--ANESTHETIC COMPARISONS FOR FOUR HIGH-DEATH-RATE OPERATIONS AFTER ADJUSTMENT FOR AGE AND PHYSICAL STATUS OBTAINED BY APPLYING SIGNED RANK TESTS TO INDIRECT STANDARDIZED MORTALITY RATIOS WITHIN INSTITUTIONS*

Ranks based on variability of contrast**

	Operation 12					Operation 33			
	N-B	C	E	O		N-B	C	O
H	1.55	-0.53	1.96	-0.12	H	-0.59	-0.25	0.03
N-B		-1.34	-0.37	-1.59	N-B		-0.26	0.77
C			-1.00	0.45	C			0.41
E				-1.36				

	Operation 44					Operation 48			
	N-B	C	E	O		N-B	C	E	O
H	-0.44	-1.77	0.15	-0.05	H	1.68	-1.06	0.52	-0.04
N-B		-1.65	0.41	-1.49	N-B		-0.23	-0.28	-0.04
C			0.91	0.44	C			0.23	-0.70
E				0.11	E				-0.93

Ranks based on size of contrast***

	Operation 12					Operation 33			
	N-B	C	E	O		N-B	C	O
H	2.21	0	1.68	0.12	H	-0.87	-1.07	-0.80
N-B		-1.34	0	-1.36	N-B		0.36	0.65
C			-1.00	-0.45	C			0.30
E				-1.57				

	Operation 44					Operation 48			
	N-B	C	E	O		N-B	C	E	O
H	-0.80	-2.12	0.81	-1.27	H	1.08	-1.34	0.25	-0.86
N-B		-0.12	1.73	-0.44	N-B		-1.45	-0.91	-0.78
C			2.04	0.47	C			-0.06	-0.06
E				-1.67	E				-0.52

Number of institutions entering into comparison

	Operation 12					Operation 33			
	N-B	C	E	O		N-B	C	O
H	21	3	8	19	H	13	10	13
N-B		2	4	15	N-B		10	9
C			1	2	C			9
E				6				

	Operation 44					Operation 48			
	N-B	C	E	O		N-B	C	E	O
H	22	26	18	27	H	20	21	13	20
N-B		19	14	19	N-B		21	15	20
C			15	25	C			15	23
E				18	E				16

* A positive number means that the agent shown in the row had a higher ISMR than the agent shown in the column; the significance of the difference can be ascertained by referring to a normal table.

** "Variability" means variance of $(\log \text{ISMR}_\alpha - \log \text{ISMR}_\beta)$, where α and β denote the agent pair. Largest rank given to smallest variance.

*** "Size of contrast" means $|\log \text{ISMR}_\alpha - \log \text{ISMR}_\beta|$. Largest rank given to largest such absolute difference.

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TABLE 20.--INDIRECT STANDARDIZED MORTALITY RATIOS (BASED ON AGE-RISK-OPERATION AGGREGATION STRATA) AND RELATED STATISTICS FOR 34 INSTITUTIONS (MIDDLE-DEATH-RATE OPERATIONS ONLY)

Inst.	Indirect SMR	Deaths D	Standard deaths $\hat{D}$	$D - \hat{D}$	$\sigma^2 = \text{Var}(D-\hat{D})$	σ	$\frac{D-\hat{D}}{\sigma}$
1	0.7286	185	254	-68[a]	1109.36	33.31	-2.041
2	1.3221	446	337	109	991.59	31.49	3.255*
3	0.8619	122	142	-19	398.03	19.95	-0.953
4	1.1324	452	399	53	1943.11	44.08	1.202
5	1.5633	724	463	261	2549.52	50.49	5.169*
6	0.8952	219	245	-25	888.91	29.81	-0.839
7	1.5979	318	199	119	705.83	26.57	4.478*
8	0.6834	632	925	-292	7023.43	83.81	-3.484
9	0.7582	519	685	-165	5129.44	71.62	-2.304
10	1.2738	501	393	108	1619.86	40.25	2.683*
11	0.7121	296	416	-119	1546.03	39.32	-3.026
12	1.1641	297	255	42	864.68	29.41	1.478
13	1.4877	150	101	49	196.22	14.01	3.498*
*14	0.5771	90	156	-65	472.83	21.74	-2.990
15	1.0351	367	355	12	1916.01	43.77	0.274
16	1.3380	296	221	75	688.52	26.24	2.858*
*17	0.8583	106	124	-17	284.46	16.87	-1.008
18	0.8384	191	228	-36	493.47	22.21	-1.621
19	1.0609	231	218	13	623.94	24.98	0.520
20	1.0213	444	435	9	2067.50	45.47	0.198
21	0.7695	459	596	-136	4526.47	67.28	-2.021
22	1.1257	384	341	43	1552.70	39.40	1.091
*23	0.5741	48	84	-35	190.09	13.79	-2.538
24	1.4329	441	308	133	1065.23	32.64	4.075*
25	1.3756	398	289	109	818.95	28.62	3.808*
26	0.9426	243	258	-14	1339.71	36.60	-0.382
27	0.9400	142	151	-8	510.21	22.59	-0.354
*28	0.7056	13	18	-4	24.44	4.94	-0.810
*29	0.8416	65	77	-11	127.06	11.27	-0.976
30	0.7379	90	122	-31	178.69	13.37	-2.319
*31	1.7667	104	59	45	154.40	12.43	3.620*
32	0.7576	139	183	-43	490.86	22.16	-1.940
33	0.7928	379	478	-98	2902.38	53.87	-1.819
*34	1.2088	132	109	23	257.23	16.04	1.434

a Negative numbers are smaller in absolute value by 1 than they should be because of the computer's treatment of rounding. These are not important because they are not used in the line of argument.

Generally, the institutional variation appears to be least for that part of the data comprising only the middle-death-rate operations. The largest-to-smallest ratios for the other analyses are: high-death-rate operations, 6.8; middle- and high-death-rate operations, 3.3; operation 12 (craniotomy), 20.5; operation 33 (heart with pump), 10.2; operation 44 (exploratory laparotomy, etc.), 12.4; and operation 48 (large bowel), 16.5.

Consider now Table 20. For the middle-death-rate operations, it shows for each institution the indirectly standardized mortality ratio (agreeing with that in Table 12), the number of actual deaths, and the figure labeled "standard deaths," calculated by applying the whole-Study death rates for the 15 age-risk-operation strata to the number of estimated exposed in those strata for the particular institution. The next column is the difference between the actual deaths and the "standard deaths." It is a positive number where there were more actual deaths. From that column, we are able to get some idea of how many deaths were involved in institutional variation. To assess the statistical significance of entries in this column, we need an estimate of the standard error of such a statistic. The next two columns, labeled "σ^2" and "σ," present the square of the standard error of $D - \hat{D}$ and the standard error itself. The last column is computed as $D - \hat{D}$ divided by its standard error. Where this number is large, we may suspect a real institutional effect;* if it exceeds 2, it is starred.

Table 21 displays the values of $(D - \hat{D})/\sigma$ for all seven analyses, again with values exceeding 2 starred. Before discussing this summary

*Appendix 1 presents a derivation of the estimate of σ. The discussion refers to the estimation of σ for Table 25, but the argument is the same for both cases.

TABLE 21.--STANDARDIZED DIFFERENCES BETWEEN DEATHS AND "STANDARD" DEATHS BASED ON AGE-RISK-OPERATION STRATA FOR SEVEN PARTS OF THE DATA

	D-$\hat{D}$						
Inst.	Middle-death-rate operations	High-death-rate operations	Middle- and high-death-rate operations	Operation 12	Operation 33	Operation 44	Operation 48
1	-2.041	0.712	-1.555	0.962	1.000	0.661	-0.500
2	3.255*	-0.692	2.160*	1.103	-0.244	-0.440	-0.598
3	-0.953	-0.335	-0.844	3.125*	-0.467	-0.331	-1.636
4	1.202	-0.480	0.425	-1.128	-0.565	1.212	0.995
5	5.169*	2.614*	5.572*	1.070	0.266	1.803	3.505*
6	-0.839	0.317	-0.310	1.240	0	-0.268	-0.102
7	4.478*	1.848	4.404*	-0.612	4.245*	2.166*	0.830
8	-3.484	-1.166	-3.413	-0.486	-0.043	-1.855	-0.359
9	-2.304	-0.162	-1.683	1.585	0.102	-0.811	0.623
10	2.683*	-3.268	-1.165	-2.144	-2.647	-0.501	-0.699
11	-3.026	-0.543	-2.651	0.251	0.400	-0.680	-0.927
12	1.478	2.493*	2.536*	2.742*	0.618	0.965	0.329
13	3.498*	4.591*	5.866*	2.823*	0.265	3.393*	3.088*
*14	-2.990	-1.398	-3.557	1.305	-0.631	-2.002	1.200
15	0.274	1.045	1.234	0.504	0.592	0.691	2.629*
16	2.858*	-0.814	1.514	-1.942	-0.129	-0.268	1.587
*17	-1.008	-0.369	-1.257	-1.110	0.640	0.446	-0.448
18	-1.621	-1.173	-1.904	-1.826	0.796	-0.568	-0.444
19	0.520	1.374	1.379	0.533	2.588*	-0.208	-1.138
20	0.198	-0.785	-0.298	-0.888	6.851*	-0.725	-1.650
21	-2.021	-1.935	-2.621	-0.939	-1.851	-0.418	-0.468
22	1.091	2.822*	1.865	3.108*	0.229	5.196*	0.450
*23	-2.538	0.362	-1.675	0.227	-1.044	1.018	0.647
24	4.075*	4.461*	6.187*	0.061	4.223*	2.243*	2.706*
25	3.808*	1.359	3.604*	2.161*	0.513	0	0.660
26	-0.382	1.023	0.294	0	1.671	3.203*	-0.706
27	-0.354	1.524	0.491	1.253	3.000*	0.391	0.126
*28	-0.810	-1.034	-1.571	-0.938	0	0	0
*29	-0.976	1.550	0.560	0.571	1.747	1.100	0
30	-2.319	-2.580	-3.351	-2.516	-1.804	0.175	0.926
*31	3.620*	3.386*	5.281*	2.519*	0.610	1.546	2.187*
32	-1.940	-1.223	-1.903	-0.758	-1.552	0.686	-0.273
33	-1.819	-1.669	-2.340	4.088*	-2.677	-1.879	-0.907
34	1.434	2.100*	2.099*	0	0	1.781	1.073

table further, we turn to a second approach to studying institutional variation in death rates.

The analyses of this section thus far have been based on rather complicated statistical procedures. To examine more directly the indicated institutional fluctuations, six operations were chosen† that generally defined particular procedures, rather than collections of procedures. The chosen operation codes were: 40, gall bladder; 45, gastric resection; 65, hysterectomy; 73, cystoscopy; 86, open reduction of the femur; and 99, thoracic or lumbar laminectomy. As a set, these operations involved 1844 deaths (about 11 percent of the 16,840 deaths in the entire Study) and 141,914 estimated exposed (about 16 percent of the 856,000 in the entire Study). Table 22 shows the estimated exposed for these six operations, by institution; Table 23, the deaths similarly classified; and Table 24, the death rates. The last two columns of Table 24 are labeled "P" and "P*"; the former is the crude death rate (calculated as D/(D+EE)) for the six operations, and the latter is the death rate after standardization for frequency of the six operations in the entire Study. This standardization evens out the effects on the death rates arising from the different frequencies of the more serious operations in individual institutions. Table 24 shows that the standardized death rate P* for these six operations has a large range of variation, reaching below 0.007 in institutions 8, 14, 23, 27, and 28, and above 0.0500 in institution 25. These standardized death rates for these six operations are plotted in Fig. 1 against the logarithm of hospital size, as measured in EE for all operations. Slightly detached from the graph, at the left, is the marginal distribution of death rates, and below the graph, the marginal distribution of EE (logarithmically scaled). Study of the death rates, on the left-hand scale, shows strikingly that they are (in the main) rather uniformly spread between 0.0047 and 0.0181, with rates for eight remaining institutions appearing to be "out of the distribution," ranging

†By John P. Bunker and William H. Forrest.

TABLE 22.--ESTIMATED EXPOSED FOR SIX SELECTED OPERATIONS, DISPLAYED BY INSTITUTION

Inst.	Operation code						
	40	65	72	99	45	86	SUM
1	945	2868	860	456	587	521	6257
2	277	454	100	77	277	262	1447
3	284	935	1138	589	447	264	3657
4	416	1298	171	710	441	318	3354
5	327	2995	871	136	572	490	5391
6	230	2402	2070	358	307	230	5597
7	339	723	271	79	271	226	1909
8	1939	3879	4401	3953	2014	373	16559
9	731	1966	2834	1143	869	777	8320
10	438	779	536	365	609	244	2971
11	259	1321	566	236	590	212	3184
12	293	2323	691	272	460	293	4332
13	98	25	215	283	682	129	1432
14	72	772	6030	169	314	72	7429
15	1168	1688	1506	779	545	493	6179
16	229	458	714	215	215	162	1993
17	66	574	722	607	148	66	2183
18	332	332	57	276	235	146	1378
19	288	1130	399	554	355	44	2770
20	1535	3188	2440	512	1220	157	9052
21	857	2969	4568	1542	1428	971	12335
22	442	1873	2055	1092	442	390	6294
23	183	398	112	41	489	41	1264
24	141	322	154	887	373	154	2031
25	97	253	253	45	282	602	1532
26	612	1803	4764	290	354	193	8016
27	72	1109	193	578	362	265	2579
28	100	301	521	13	107	27	1069
29	27	113	145	86	96	107	574
30	6	79	112	34	11	17	259
31	218	207	459	92	172	46	1194
32	207	700	207	220	376	272	1982
33	357	439	3648	302	274	165	5185
34	194	347	51	674	143	797	2206
SUM	13779	41023	43854	17665	16067	9526	

TABLE 23.--DEATHS FOR SIX SELECTED OPERATIONS DISPLAYED BY INSTITUTION

Inst.	Operation code 40	65	72	99	45	86	SUM
1	5	4	3	3	27	11	53
2	16	2	4	3	47	30	102
3	1	1	6	0	17	7	32
4	5	4	3	6	26	15	59
5	14	11	10	8	62	71	176
6	5	5	3	3	21	10	52
7	16	7	2	5	35	27	92
8	9	9	5	10	51	11	95
9	6	6	5	2	30	16	65
10	9	2	7	4	33	24	79
11	0	6	3	3	15	0	27
12	3	3	5	6	19	5	41
13	1	0	1	4	17	3	26
14	1	2	5	2	4	1	15
15	11	5	7	5	38	34	100
16	2	2	5	2	9	4	24
17	0	3	2	5	5	2	17
18	3	2	1	0	15	7	28
19	1	4	3	1	11	2	22
20	11	6	12	8	48	9	94
21	8	4	5	9	47	26	99
22	2	4	10	5	28	8	57
23	1	0	0	1	5	0	7
24	4	7	9	7	46	6	79
25	7	0	10	3	47	72	139
26	9	2	11	1	26	9	58
27	0	2	0	4	13	5	24
28	0	1	1	0	2	1	5
29	0	0	2	0	3	2	7
30	0	3	3	1	0	1	8
31	2	0	5	0	13	3	23
32	2	0	1	1	15	5	24
33	7	2	15	11	29	8	72
34	0	3	0	2	13	25	43
SUM	161	112	169	125	817	460	

TABLE 24.--DEATH RATES, D/D+EE, FOR SIX SELECTED OPERATIONS DISPLAYED BY INSTITUTION

Inst.	Operation code 40	65	72	99	45	86	P	P*
1	0.00526	0.00139	0.00340	0.00654	0.04397	0.02068	0.00840	0.00936
2	0.05461	0.00439	0.03846	0.03750	0.14506	0.10274	0.06585	0.04714
3	0.00351	0.00107	0.00524	0.00000	0.03664	0.02583	0.00867	0.00835
4	0.01188	0.00307	0.01724	0.00838	0.05567	0.04505	0.01729	0.01802
5	0.04106	0.00366	0.01135	0.05556	0.09779	0.12656	0.03161	0.03566
6	0.02128	0.00208	0.00385	0.00831	0.06402	0.04167	0.00921	0.01528
7	0.04507	0.00959	0.00733	0.05952	0.11438	0.10672	0.04598	0.03757
8	0.00462	0.00231	0.00113	0.00252	0.02470	0.02865	0.00570	0.00666
9	0.00814	0.00304	0.00176	0.00175	0.03337	0.02018	0.00775	0.00774
10	0.02013	0.00256	0.01289	0.01084	0.05140	0.08955	0.02590	0.02023
11	0.00000	0.00452	0.00527	0.01255	0.02479	0.00000	0.00841	0.00737
12	0.01014	0.00129	0.00718	0.02158	0.03967	0.01678	0.00938	0.01205
13	0.01010	0.00000	0.00463	0.01394	0.02432	0.02273	0.01783	0.00856
14	0.01370	0.00258	0.00083	0.01170	0.01258	0.01370	0.00202	0.00620
15	0.00933	0.00295	0.00463	0.00638	0.06518	0.06452	0.01593	0.01609
16	0.00866	0.00435	0.00695	0.00922	0.04018	0.02410	0.01190	0.01175
17	0.00000	0.00520	0.00276	0.00817	0.03268	0.02941	0.00773	0.00923
18	0.00896	0.00599	0.01724	0.00000	0.06000	0.04575	0.01991	0.01809
19	0.00346	0.00353	0.00746	0.00180	0.03005	0.04348	0.00788	0.01040
20	0.00712	0.00188	0.00489	0.01538	0.03785	0.05422	0.01028	0.01284
21	0.00925	0.00135	0.00109	0.00580	0.03186	0.02608	0.00796	0.00789
22	0.00450	0.00213	0.00484	0.00456	0.05957	0.02010	0.00897	0.01149
23	0.00543	0.00000	0.00000	0.02381	0.01012	0.00000	0.00551	0.00466
24	0.02759	0.02128	0.05521	0.00783	0.10979	0.03750	0.03744	0.04214
25	0.06731	0.00000	0.03802	0.06250	0.14286	0.10682	0.08318	0.05010
26	0.01449	0.00111	0.00230	0.00344	0.06842	0.04455	0.00718	0.01398
27	0.00000	0.00180	0.00000	0.00687	0.03467	0.01852	0.00922	0.00672
28	0.00000	0.00331	0.00192	0.00000	0.01835	0.03571	0.00466	0.00617
29	0.00000	0.00000	0.01361	0.00000	0.03030	0.01835	0.01205	0.00900
30	0.00000	0.03659	0.02609	0.02857	0.00000	0.05556	0.02996	0.02585
31	0.00909	0.00000	0.01078	0.00000	0.07027	0.06122	0.01890	0.01669
32	0.00957	0.00000	0.00481	0.00452	0.03836	0.01805	0.01196	0.00872
33	0.01923	0.00454	0.00410	0.03514	0.09571	0.04624	0.01370	0.02322
34	0.00000	0.00857	0.00000	0.00296	0.08333	0.03041	0.01912	0.01472

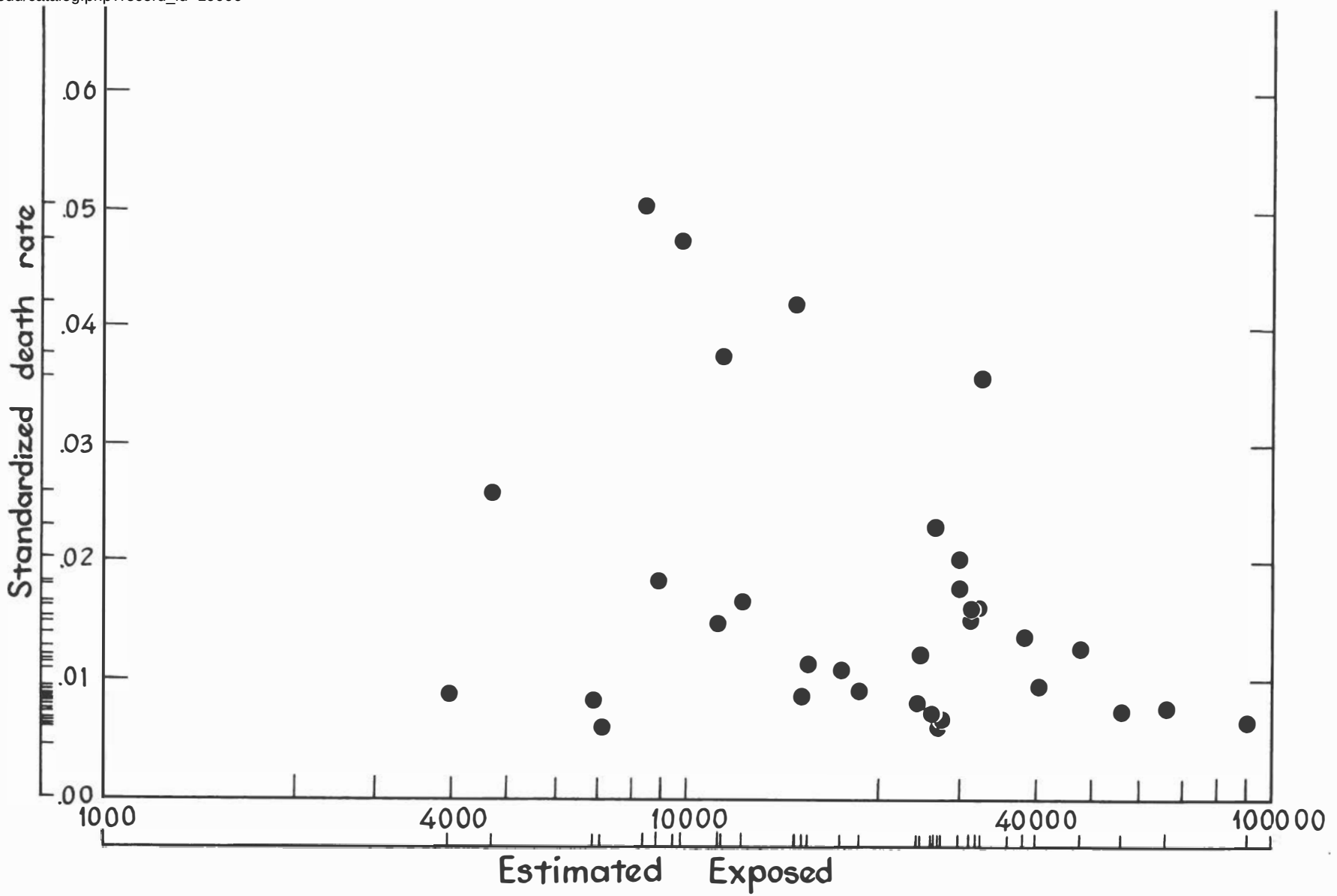

Figure 1.--Standardized death rates for six operations plotted against logarithm of hospital size as measured in EE for all operations.

TABLE 25.--COMPARISON OF OBSERVED AND FITTED DEATHS FOR SIX OPERATIONS IN EIGHT INSTITUTIONS IN WHICH THE SIX-OPERATION DEATH-RATE EXCEEDED 0.02

Inst.	D=Actual deaths	$\hat{D}$=Standard deaths	$D-\hat{D}$	Var $\hat{D}$	$\hat{\sigma}_{(D-\hat{D})}$	$\frac{D-\hat{D}}{\hat{\sigma}_{D-\hat{D}}}$
2	102	32.2	69.8	10.6	10.6	6.58
5	176	69.1	106.9	73.7	15.8	6.78
7	92	32.2	69.8	14.6	10.3	6.79
10	79	54.6	24.4	54.2	11.5	2.12
24	79	36.2	42.8	18.1	9.9	4.32
25	139	46.5	92.5	16.5	12.5	7.40
30	8	2.35	5.65	0.41	2.9	1.95
33	72	43.6	28.4	33.6	10.3	2.76
Total	747	316.8				

from 0.02 to 0.05. These eight are institutions 2, 5, 7, 10, 24, 25, 30, and 33. Table 25 shows for the eight institutions information like that in Table 20.

We are now in a position to tie together the diverse information about the statistical significance of the larger discrepancies between observed and "standard" deaths. We have identified institutions with large differences in seven different ways: each of six analyses* based on age-risk-operation strata yielded some institutions for which $(D-\hat{D})/\sigma$ exceeded 2; the panel of six operations (four of which belong to the middle-death-rate group and two of which belong to the low-death-rate group) identified eight institutions with large-looking death rates for that panel of operations. We can now, by turning to Tables 21 and 25, list all institutions among the 34 that have ever been indicated as "high," and display the values of $(D-\hat{D})/\sigma$ leading to the indication. Table 26 summarizes these findings.

The first column shows the institutions that have come to notice in any of the analyses. The next three columns are the most important. The fourth is based on data independent of the second and third, which are themselves somewhat interdependent through sharing four operations, but otherwise are quite different. The last four columns supplement the fourth for those readers who may prefer not to combine the four high-death-rate operations. The panel of six operations involves no adjustments for age or risk. The reason for displaying these figures is that we have some diffidence about accepting a large value of $(D-\hat{D})/\sigma$ as indicating statistically significant institutional effects. But if the same institutions are indicated in different and independent analyses, then considerable strength is gained.

*We ignore the middle- and high-death-rate analysis because of its overlap with other analyses.

Table 26 shows that 20 of the 34 institutions have in some place exhibited a high value of $(D-\hat{D})/\sigma$. Of these, eight have appeared but once; their institution identification numbers are circled. We dismiss these as probably signifying nothing of importance. More data are represented in the middle-death-rate group than in either the panel of six operations or the high-death-rate group. Of the nine institutions where $(D-\hat{D})/\sigma$ exceeds 2 for the middle-death-rate operations, only one (institution 16) was dismissed above for noncorroboration. Six of the remaining eight institutions are also members of the eight outliers for the panel of six operations. Finally, in four cases (five if we count institution 7), there is a match with identification by the high-death-rate operations analysis as an outlier. In all, eight institutions are identified by the middle-death-rate operations and also by the high-death-rate operations or the panel of six, or both: institutions 2, 5, 7, 10, 13, 24, 25, and 31 (these are starred in Table 26). We conclude that the consistent appearance of these institutions as outliers demonstrates heterogeneity of indirectly standardized mortality ratios to an extent calling for some explanation other than sampling error.

Several questions present themselves. Given that some large part of the institutional variation is real, of what practical consequence is it? Did dozens, hundreds, or thousands of deaths occur in the few hospitals with notably high death rates? After gauging the practical size of the apparent institutional effects, what conclusions, if any, are warranted about appropriate steps to take?

We turn now to an investigation of these questions.

The sum of the positive values of $D-\hat{D}$ for the middle- and high-death-rate operations together was about 1750, as was the sum of the negative values. (The number expected by chance

TABLE 26.--SUMMARY OF EXTREME POSITIVE VALUE OF $\frac{D-\hat{D}}{\sigma}$ FROM TABLES 21 AND 25

Inst.	Panel of six operations	Middle-death-rate operations	High-death-rate operations	Operation 12	Operation 33	Operation 44	Operation 48
*2	6.58	3.255					
③				3.125			
*5	6.78	5.169	2.614				3.505
*7	6.79	4.478			4.245	2.166	
*10	2.12	2.683	(-3.268)	(-2.144)	(-2.647)		
12			2.493	2.742			
*13		3.498	4.591	2.823		3.393	3.088
⑮							2.629
⑯		2.858					
⑲					2.588		
⑳					6.851		
22			2.822	3.108		5.196	
*24	4.32	4.075	4.461		4.223	2.243	2.706
*25	7.40	3.808		2.161			
㉖						3.203	
㉗					3.000		
30	1.95	(-2.319)	(-2.580)	(-2.516)			
*31		3.620	3.386	2.519			2.187
33	2.76			4.088	(-2.677)		
㉞			2.100				

is in the range 435 to 525.) Involved here, in each direction, is about one-tenth of the number of deaths in the whole Study. Of course, a total of 1750 deaths is enormous in comparison with the number of deaths attributable to hepatic necrosis, but may or may not be regarded as importantly large when related to a total of 490,000 surgical procedures in the middle- and high-death-rate groups.

At this point, we are forced to conclude that the differences between observed deaths and estimates of what they might be are, in many institutions, real and importantly large. But these differences are very difficult to interpret because "standard deaths," our estimate of "what they might be," cannot receive our unreserved confidence. These estimates are based on statistical adjustments, taking some account of operation, age, and physical status, but the adjustments may be incomplete and, more importantly, no account has been taken of other variables that might be very important. Among such possible important considerations are a differential willingness to undertake operations that look risky and a differential selection of difficult cases in certain hospitals. We have not looked at medical deaths and do not know how to. In some hospitals with surgical death rates that look high in our data, there might be a degree of surgical enterprise resulting not only in many more surgical deaths, but also in an unseen substantial decrease in what would otherwise be recorded as mortality belonging to the medical wards. The fact is that we can point to unexplained differences, but we do not have the evidence to claim, where one institution is "high" and another is "low" in our data, that the latter is "better." That, of course, is one possibility, but other possibilities are that these two institutions would be found to be equal, or even in reverse order, if comparisons on thoroughly equivalent surgical cases were to be made, or if net medical gain to the total population of patients--medical and surgical--were measured.

We are able to summarize our findings on institutional differences in the following way:

(1) There are numerous institutions in which the numbers of actual deaths differ from the numbers of estimated deaths by several times their standard errors, and these differences cannot be regarded as due to randomness in the data.

(2) For each institution where such a large difference occurs, there is posed a question: "What accounts for this difference?"

(3) The presence of this question does not necessarily indicate that the particular institution has inferior surgical performance. It is naturally important to understand better whether this is or is not the case for the outlying institutions.

(4) The question of what steps, if any, should be taken in the further elucidation of these unexplained institutional peculiarities is difficult to answer. Some indications of how further statistical analysis may illuminate the problem are given in Appendix 2. Questions of administrative feasibility and related matters are discussed in Chapter IV-8.

APPENDIX 1 TO CHAPTER IV-6

EXAMINING THE STANDARD ERRORS

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Tables 20, 21, and 25 of Chapter IV-6 present values of $D_j - \hat{D}_j$ and of estimated standard errors for such quantities. The formula used for computation of the values in those tables appears below as Eq. 11. That formula is an approximation to the variance. Its derivation uses the assumption that the deaths for each operation in each institution, and the randoms for each operation in each institution, are mutually independent Poisson random variables. The derivation also neglects certain terms in the correct expression for the variance. (The neglected terms are of opposite effect and will in some measure offset each other.) Finally, expected values of Poisson random variables are replaced by their observed values.

This appendix presents the derivation, considers the sizes of the neglected terms, and exhibits them for the data of Table 25; it also presents evidence on the assumption that the deaths and randoms behave as Poisson random variables.

The formulas are developed in terms of six strata, one corresponding to each of the special operations. In the case of the age-operation-risk strata used in Tables 20 and 21, there are 15 strata.

DEVELOPMENT OF FORMULAS

Define R_{ij} as the number of patients in the random sample from institution j who proved to be exposed to operation i. Similarly, define D_{ij} as the number of deaths from operation i observed in institution j. Let k_j denote the "blowup factor" in institution j. In each case, in our example, $j = 1,\ldots,34$ and $i = 1,\ldots,6$.

Then we define:

the estimated exposed for operation i in institution j as	$EE_{ij} = k_j R_{ij}$,
the estimated death rate for operation i over all institutions as	$p_i = \dfrac{\sum_j D_{ij}}{\sum_j EE_{ij}}$,
the observed deaths for institution j (for the six operations) as	$D_j = \sum_i D_{ij}$, (1)
the "estimated" deaths for operation i in institution j as	$\hat{D}_{ij} = p_i \widehat{EE}_{ij} = p_i k_j R_{ij}$, and
the "estimated" deaths for all six operations in institution j as	$\hat{D}_j = \sum_i \hat{D}_{ij}$.

It is our aim to evaluate $\mathrm{Var}\,(D_j - \hat{D}_j)$.

In the sequel we shall affix a superscript asterisk to the symbol for a random variable to denote its expectation. Thus, D^*_{ij} means $E(D_{ij})$.

$$\mathrm{Var}\,(D_j - \hat{D}_j) = \mathrm{Var}\,D_j - 2\,\mathrm{cov}\,(D_j, \hat{D}_j) + \mathrm{Var}\,\hat{D}_j. \qquad (2)$$

The first term is equal (under the Poisson assumption) to D_j^*. We now develop an expression for the third term under the Poisson assumption.

$$\text{Var}(\hat{D}_j) = \text{Var}\left(\sum_i p_i k_j R_{ij}\right)$$

$$= k_j^2 \sum_i \left[(p_i^*)^2 \text{ Var}(R_{ij}) + 2p_i^* R_{ij}^* \text{ cov}(p_i, R_{ij}) + R_{ij}^{*2} \text{ Var}(p_i) \right] \quad (3)$$

$$= k_j^2 \sum_i \left[(p_i^*)^2 R_{ij}^* + 2p_i^* R_{ij}^* \text{ cov}(p_i, R_{ij}) + R_{ij}^{*2} \text{ Var}(p_i) \right].$$

To proceed further, we need to evaluate Var (p_i) and cov (p_i, R_{ij}).

$$\text{Var}(p_i) = \text{Var} \frac{\sum_j D_{ij}}{\sum_j EE_{ij}} = \text{Var} \frac{\sum_j D_{ij}}{\sum_j k_j R_{ij}}.$$

Applying the usual formula for the variance of a ratio and observing that the variance of a Poisson random variable equals its mean, we obtain:

$$\text{Var}(p_i) = (p_i^*)^2 \left\{ \frac{\sum_j D_{ij}^*}{(\sum_j D_{ij}^*)^2} + \frac{\sum_j k_j^2 R_{ij}^*}{(\sum_j k_j R_{ij}^*)^2} \right\}. \quad (4)$$

Now define

$$W_{ij} = \frac{k_j R_{ij}^*}{\sum_j k_j R_{ij}^*}, \quad \text{noting that } \sum_j W_{ij} = 1, \text{ and} \quad (5)$$

$$\overline{K}_i = \sum_j W_{ij} k_j . \quad (6)$$

These enable us to rewrite the expression for Var (p_i) as:

$$\text{Var}(p_i) = (p_i^*)^2 \left\{ \frac{1}{\sum D_{ij}^*} + \frac{\overline{K}_i}{\sum_j k_j R_{ij}^*} \right\}. \quad (7)$$

We must now evaluate cov (p_i, R_{ij}).

$$\text{cov}(p_i, R_{ij}) = \text{cov}\left(\frac{\sum_j D_{ij}}{\sum_j k_j R_{ij}}, R_{ij} \right) = \left(\sum_j D_{ij}^* \right) \left(- \frac{k_j R_{ij}^*}{(\sum_j k_j R_{ij}^*)^2} \right)$$

$$= - \left(\frac{W_{ij}}{\sum_j k_j R_{ij}^*} \right) (\sum_j D_{ij}^*) = -p_i^* W_{ij} . \quad (8)$$

Substituting Eqs. 7 and 8 into Eq. 3, we have:

$$\text{Var}(\hat{D}_j) = k_j^2 \sum_i \left[(p_i^*)^2 R_{ij}^* - 2(p_i^*)^2 R_{ij}^* W_{ij} + (R_{ij}^*)^2 (p_i^*)^2 \left\{ \frac{1}{D_{ij}^*} + \frac{\overline{K}_i}{\sum_j k_j R_{ij}^*} \right\} \right]. \quad (9)$$

Now we replace expectations by their observed values and, using the definitions in Eqs. 1, obtain the estimated variance:

$$\hat{\text{Var}}\,(\hat{D}_j) = \sum_i \left\{ k_j p_i \hat{D}_{ij} - 2p_i^2 k_j^2 R_{ij} W_{ij} + \hat{D}_{ij}^2 \left(\frac{1}{\sum_j D_{ij}} + \frac{\bar{K}_i}{\sum_j EE_{ij}} \right) \right\} . \qquad (10)$$

Now, because $\sum_j \hat{D}_{ij} = \sum_j D_{ij}$, we may write:

$$\hat{D}_{ij} = \hat{\xi}_{ij} \sum_j D_{ij} \quad \text{and note} \quad \sum_j \hat{\xi}_{ij} = 1 ,$$

which enables rewriting Eq. 10 as:

$$\hat{\text{Var}}\,(\hat{D}_j) = \sum_i \hat{D}_{ij} (k_j p_i - 2p_i k_j W_{ij} + \hat{\xi}_{ij} + \bar{K}_i p_i \hat{\xi}_{ij}). \qquad (11)$$

The last three terms in the parentheses are small, compared with the first. k_j is a number like 20 or 25 (and so is $\bar{K}_i$, a weighted average of the k_j, the weights depending on i); p_i is a number like 0.01. The 34 values of $\hat{\xi}_{ij}$ add to 1, and they are numbers like 0.03. The same is true of W_{ij}. In all, we conclude that omission of the three later terms should result in an error that is not serious. The estimate of Var $(D_j - \hat{D}_j)$ used in Table 26 was:

$$\hat{\text{Var}}\,(D_j - \hat{D}_j) = D_j + k_j \sum_i p_i^2 EE_{ij} , \qquad (12)$$

which is obtained from Eq. 2 by neglecting the terms in Eq. 11 as just discussed, by estimating D_j^* the variance of D_j by its observed value, D_j, and by ignoring the covariance term in Eq. 2. We now study the actual magnitude of the covariance term.

Recall that

$$\hat{D}_j = \sum_i EE_{ij} p_i = \sum_i k_j R_{ij} \frac{\sum_j D_{ij}}{\sum_j k_j R_{ij}} .$$

By defining

$$U_{ij} = \frac{k_j R_{ij}}{\sum_j k_j R_{ij}}$$

(note $\sum_j U_{ij} = 1$) and

$$D_{i+} = \sum_j D_{ij} ,$$

we may write:

$$\hat{D}_j = \sum_i U_{ij} D_{i+} .$$

Then

$$\text{cov}\,(D_j, \hat{D}_j) = \text{cov}\,(\sum_i D_{ij}, \sum_i U_{ij} D_i^+) = \sum_i U_{ij}^* \text{Var}\, D_{ij} .$$

This we estimate as:

$$\hat{c}ov\,(D_j, \hat{D}_j) = \sum_i U_{ij} D_{ij} \quad . \tag{13}$$

Because it is easily shown that $U_{ij} = \hat{\xi}_{ij}$, we write this as:

$$\hat{c}ov\,(D_j, \hat{D}_j) = \sum_i \hat{\xi}_{ij} D_{ij} \quad . \tag{14}$$

This neglected term is comparable in size with what was neglected in Eq. 10; it has the coefficient -2 in the true expression for Var $(D_j - \hat{D}_j)$.

Entering into Eq. 2 the expression D_j for the first term, the covariance term from Eq. 14, and the value of $\hat{V}ar\,(\hat{D}_j)$ given in Eq. 11, we obtain the full expression for the estimated variance:

$$\hat{V}ar\,(D_j - \hat{D}_j) = D_j - 2 \sum_i \hat{\xi}_{ij} D_{ij} + \sum_i \hat{D}_{ij} (k_j p_i - 2 p_i k_j W_{ij} + \hat{\xi}_{ij} + \overline{K}_i p_i \hat{\xi}_{ij}) \quad , \tag{15}$$

and, by writing $\sum_i \hat{D}_{ij} k_j p_i$ as $k_j \sum_i p_i^2 EE_{ij}$, we may exhibit the expression above as two parts--the two-term approximation used in Tables 21 and 26, plus the neglected terms:

$$\hat{V}ar\,(D_j - \hat{D}_j) = \left\{ D_j + k_j \sum p_i^2 EE_{ij} \right\} - \left\{ 2 \sum_i \hat{\xi}_{ij} D_{ij} + \sum \hat{D}_{ij} (2 p_i k_j W_{ij} - \hat{\xi}_{ij} - \overline{K}_i p_i \hat{\xi}_{ij}) \right\} \quad . \tag{16}$$

In Table 1 of this appendix, we display all the terms in Eq. 16 for the 34 institutions on the six-operation data. The third column displays the approximation; the last column, the complete expression. In general, the approximate expression slightly exceeds the complete sum, and we conclude that the approximation is good.

THE POISSON ASSUMPTION

The occurrence of a death in a particular hospital from a specified operation is in any short period an event of small probability. It is plausible that the probability of such an event is proportional to the brief time of observation, and that the occurrence of more than one such death in a brief period has, in comparison, a negligible probability. If, further, events in nonoverlapping intervals are independent, we should have a correspondence with the axioms for a Poisson process, and it would be reasonable to expect the deaths in a fixed period to be observations on a Poisson random variable.

In the case of the randoms, we took, in each month for each hospital, a fixed (almost) number of cases at random (almost) from the month's surgical load. With any particular operation, there is associated a small probability that a random case will be exposed to that operation. Altogether, our six operations involved 16 percent of the exposures. The typical monthly sample was 25. For N = 25, p = 0.16, the binomial distribution (which is, at least plausibly, applicable) is fairly well approximated by the Poisson. Thus, we have some reason to expect approximate Poisson behavior of the randoms.

But, because experience often shows overdispersion in what might be hoped to be Poisson data, we checked both series, R_{ij} and D_{ij}, in two ways, for the six operations. The first approach was to study yearly totals for each of the six operations in each of the 34 hospitals. If the deaths (or randoms) were occurring as a Poisson process during the 4 years, and if in addition the Poisson process was

the same in all 4 years, then the statistic below should be distributed as χ^2_3 (chi-square with 3 degrees of freedom):

$$\sum_{k=1}^{4} \frac{(x_{ijk} - x_{ij\cdot})^2}{x_{ij\cdot}},$$

where $i = 1,\ldots,6$ indexes operation; $j = 1,\ldots,34$ indexes hospital; $k = 1,\ldots,4$ indexes year; and x represents deaths or randoms.

Assessing the validity of the Poisson assumption in this way may be unnecessarily stringent, for if x_{ij1}, x_{ij2}, x_{ij3}, and x_{ij4} are independent Poisson random variables with different parameters (reflecting a change in the process over time), it would be true that their sum was a Poisson random variable (the assumption with whose validity we are concerned), but the statistic proposed above would be stochastically greater than χ^2_3, casting doubt on the Poisson assumption.

The second approach taken is nearly free of the difficulty of the first. The variation from one month to the next allows the assessment of overdispersion. But the classification simultaneously by month, operation, and institution is too fine; we therefore took monthly figures for the six operations combined in each institution, defining x_{jk} to be the number of deaths (or randoms) for all six operations in hospital j for the kth one of the months 1, 3, 5,...,47 and x'_{jk} to be the corresponding figure for the kth of the months 2, 4, 6,...,48. Then if x_{jk} and x'_{jk} are independent Poisson random variables with the same parameter, the statistic below is distributed approximately as χ^2_1:

$$\frac{(x_{jk} - x'_{jk})^2}{x_{jk} + x'_{jk}}.$$

The expected value of the statistic under the Poisson assumption is exactly 1.0. This statistic also will be stochastically larger than χ^2_1 in the presence of a time-varying Poisson process. But a slow variation will induce only a small inflation in the contrast between adjacent months.

The yearly total data (Tables 2 and 3) show a degree of dispersion exceeding Poisson variation by about 40 percent for the randoms, and by about 13 percent for the deaths. Neither of these is important so far as gauging the standard error of $D_j - \hat{D}_j$ is concerned, first, because in the standard error we are dealing not with 1.40 and 1.13, but with their square roots; and, second, because no qualitative conclusion in Chapter IV-6 would be altered if all standard errors were changed by as much as half their value, let alone by less than one-fifth. Furthermore, we have already pointed out that the degree of overdispersion relevant to our standard errors may possibly be exaggerated by using results based on yearly totals.

The odd-even monthly comparisons, shown in Table 4, indicate variance exceeding the Poisson norm by 5 percent for the randoms and 10 percent for the deaths. In terms of the standard errors, these imply corrections of 2.5 percent and 5 percent to standard errors calculated on the Poisson assumption.

TABLE 1.--TERMS IN EQUATION 16 FOR THE 34 INSTITUTIONS ON THE SIX-OPERATION DATA

INST.	D_j	$k_j \Sigma p_i^2 EE_{ij}$	$\widehat{Var}(D_j - \hat{D}_j)$	$\Sigma_i \hat{D}_{ij} k_j p_i$	$-2\Sigma_i \hat{D}_{ij} k_j p_i W_{ij}$	$\Sigma_i \hat{D}_{ij} \hat{\xi}_{ij}$	$\hat{D}_{ij} k_i p_i \hat{\xi}_{ij}$	$-2\Sigma U_{ij} D_{ij}$	Sum of omitted terms	"Exact" variance of $(D_j - \hat{D}_j)$
1	53.000	95.120175	148.12018	95.12018	-8.6740	3.92262	4.04751	-4.6966	-5.40050	142.71968
2	102.000	10.556708	112.55671	10.55671	-0.4606	0.67284	0.89883	-4.0028	-2.89172	109.66499
3	32.000	37.855530	69.85553	37.85553	-2.0963	1.36517	1.61308	-1.7321	-0.85011	69.00542
4	59.000	48.620381	107.62038	48.62038	-2.9134	1.59172	1.83661	-3.4898	-2.97481	104.64557
5	176.000	73.721566	249.72157	73.72157	-6.2294	3.01433	3.45645	-14.5099	-14.26852	235.45305
6	52.000	36.491395	88.49140	36.49140	-1.6100	1.42322	0.97364	-2.9147	-2.12789	86.36350
7	92.000	14.531535	106.53154	14.53154	-0.5779	0.63254	0.77820	-3.5653	-2.73244	103.79909
8	95.000	494.828554	589.82855	494.82855	-116.0142	25.70068	25.65549	-23.3638	-88.02179	501.80677
9	65.000	195.305854	260.30585	195.30585	-25.7571	7.39044	8.52288	-7.9722	-17.81601	242.48985
10	79.000	54.444886	133.44489	54.44489	-3.7383	1.75732	2.44893	-4.7158	-4.24778	129.19711
11	27.000	49.181238	76.18124	49.18124	-3.2202	1.55302	2.18563	-1.6457	-1.12725	75.05399
12	41.000	40.884553	81.88455	40.88455	-2.3968	1.60843	1.77454	-2.2053	-1.21913	80.66542
13	26.000	12.835749	38.83575	12.83575	-0.9712	1.60077	2.58065	-1.6767	1.53349	40.36924
14	15.000	26.368425	41.36843	26.36843	-1.4320	3.58907	0.99598	-1.6705	1.48253	42.85095
15	100.000	72.486968	172.48697	72.48697	-6.4288	3.96124	3.79487	-9.2955	-7.96824	164.51872
16	24.000	13.319357	37.31936	13.31936	-0.3963	0.40110	0.45229	-0.6996	-0.24250	37.07685
17	17.000	9.689690	26.68969	9.68969	-0.1940	0.31059	0.19457	-0.6134	-0.30231	26.38739
18	28.000	8.182992	36.18299	8.18299	-0.2500	0.41447	0.48290	-0.8329	-0.18549	35.99750
19	22.000	24.406508	46.40651	24.40651	-1.0061	0.69665	0.74841	-0.8829	-0.44403	45.96248
20	94.000	150.180274	244.18027	150.18027	-21.5295	8.13826	8.99521	-12.7689	-17.16494	227.01534
21	99.000	356.317406	455.31741	356.31741	-66.4191	15.22980	17.96667	-17.8429	-51.06549	404.25192
22	57.000	57.520425	114.52042	57.52042	-3.9560	2.63777	2.32953	-4.2449	-3.23362	111.28681
23	7.000	14.182684	21.18268	14.18268	-0.8003	0.80602	1.28649	-0.3356	0.95669	22.13937
24	79.000	17.889255	96.88925	17.88925	-0.7879	0.90190	0.98784	-3.2881	-2.18629	94.70296
25	139.000	15.987892	154.98789	15.98789	-1.5088	2.10744	2.88136	-10.9792	-7.49922	147.48867
26	58.000	49.809272	107.80927	49.80927	-2.6720	3.14751	1.34113	-4.9085	-3.09181	104.71746
27	24.000	38.644854	62.64485	38.64485	-1.9042	0.99421	1.21349	-1.2340	-0.93052	61.71434
28	5.000	2.429774	7.42977	2.42977	-0.0298	0.07836	0.07261	-0.0707	0.05046	7.48024
29	7.000	2.716479	9.71648	2.71648	-0.0462	0.09349	0.12764	-0.0940	0.08095	9.79743
30	8.000	0.408404	9.40840	0.40840	-0.0011	0.00386	0.00292	-0.0343	-0.02863	8.37977
31	23.000	6.825648	29.82565	6.82565	-0.1343	0.16941	0.19055	-0.4753	-0.24964	29.57601
32	24.000	21.416328	45.41633	21.41633	-1.0754	0.91459	1.27130	-1.0820	0.02847	45.44480
33	72.000	33.304168	105.30417	33.30417	-1.3606	1.70253	0.79384	-4.5437	-3.40789	101.89627
34	43.000	23.387052	66.38705	23.38705	-3.2750	3.50703	4.47713	-4.6182	0.09106	66.47811

TABLE 2.--DISTRIBUTION OF YEARLY TOTALS X_3^2-STATISTIC FOR SIX OPERATIONS IN 34 INSTITUTIONS (RANDOMS)

Percentile interval	Interval of values	Observed frequency	Expected frequency if Poisson
0-10	0-0.584	13	20.4
10-20	0.584-1.00	15	20.4
20-30	1.00-1.42	14	20.4
30-40	1.42-1.87	20	20.4
40-50	1.87-2.37	21	20.4
50-60	2.37-2.95	12	20.4
60-70	2.95-3.67	27	20.4
70-80	3.67-4.64	11	20.4
80-90	4.64-6.25	28	20.4
90-95	6.25-7.81	16	10.2
95-99	7.81-11.3	16	8.2
99-100	13.3-∞	11	2.0
		204	204

The sum of 204 values of the statistic was 853.10, yielding an average of 4.182. This is 139.4 percent of the null expected value, which is 3.

TABLE 3.--DISTRIBUTION OF YEARLY TOTALS X_3^2-STATISTIC FOR SIX OPERATIONS IN 34 INSTITUTIONS* (DEATHS)

Percentile interval	Interval of values	Observed frequency	Expected frequency if Poisson
0-10	0-0.584	6	17
10-20	0.584-1.00	16	17
20-30	1.00-1.42	2	17
30-40	1.42-1.87	6	17
40-50	1.87-2.37	36	17
50-60	2.37-2.95	4	17
60-70	2.95-3.67	51	17
70-80	3.67-4.64	16	17
80-90	4.64-6.25	17	17
90-95	6.25-7.81	7	8.5
95-99	7.81-11.3	7	6.8
99-100	13.3-∞	2	1.7
		170	170

The sum of 170 values of the statistic was 576.12, yielding an average of 3.39. This is 113 percent of the null expected value, which is 3.

*Instead of 204 = 6 x 34 values, there are 170, because in certain institutions there were no deaths associated with some of the operations during the 4 years. In 13 institutions there was one such operation, in six there were two, and in three there were three.

TABLE 4.--DISTRIBUTION OF 34 INSTITUTIONS' AVERAGE VALUES OF SUCCESSIVE-MONTHS' X_1^2-STATISTICS (RANDOMS, DEATHS)

Midpoint of class interval	Frequencies	
	Randoms*	Deaths+
0.55	2	0
0.70	2	1
0.85	7	11
1.00	8	6
1.15	6	13
1.30	5	1
1.45	3	1
1.60	1	1

*Unweighted average of the 34 values is 1.05. Of the 801 individual values of X_1^2, 44 exceeded 3.84, the upper-5-percent point of the X_1^2 distribution, and four exceeded 6.61, the upper-1-percent point.

+Weighted average of the 34 values is 1.10. Of the 595 individual values of X_1^2, 21 exceeded 3.84, the upper-5-percent point of the X_1^2 distribution, and none exceeded 6.61, the upper-1-percent point.

APPENDIX 2 TO CHAPTER IV-6

A FURTHER INQUIRY INTO INSTITUTIONAL DIFFERENCES BY MEANS OF SUPERSTANDARDIZATION

(A REGRESSION ADJUSTMENT BEYOND STANDARDIZATION)

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This appendix develops and discusses the technique of superstandardization, as applied to institution-institution comparisons. Most of the discussion is based on an earlier standardization of death rates that is no longer considered satisfactory and that has disappeared from the text of Chapter IV-6. Because the results of this appendix were influential in precipitating the use of a better standardization, and because the existence of the better standardization allows a partially objective check on the conclusions of the earlier analysis, I have reproduced the original superstandardization analysis in essentially the form it stood in when the new standardization became available.

The original versions of the last two sections of Chapter IV-6 used a standardization based on a combination of age and shock-likelihood index (SLI), described in an earlier version in these words:

> We have applied cell aggregation to the age × SLI classification. This involves adjustment for three interfering variables, age and, through SLI, operation and whether the procedure was elective or emergency (a part of anesthetic risk classification). As in earlier applications in Chapter IV-6, the age × SLI cross-classification was swept in death-rate order into 10 categories equinumerous in terms of deaths-plus-randoms. These strata were then used for the construction of indirectly standardized mortality ratios for each agent with hospital (reference population being "all agents" in the particular hospital).

Most of this appendix (ending with "Possibilities of Further Studies") is based on the earlier standardization, which covered all operations.

OLD INTRODUCTION

The age-SLI analyses of (the old version of) the last section of Chapter IV-6 are based entirely on simple standardization over strata combining three background variables: age, operation, and the emergency or elective character of the anesthetic risk. We know that these variables, although clearly helpful, are incomplete. The riskiness of an individual administration does not depend only on what is expressed by age or class of operation and whether the operation is considered an emergency. There is also, for example, what has been summarized into other aspects of anesthetic risk.

The various stages of standardization produce large and important reductions in institution-to-institution differences of mortality, but there is no reason to suppose that these reductions are complete and final. Adjustments of this sort are never perfect, and usually fall short of complete adjustment, rather than going beyond it. In a situation, like the present one, where unadjusted differences are large in comparison with adjusted ones, failures of adjustment to be complete will typically leave accidental differences of at least the same order of magnitude as any true differences that may be present. Although these failures may make apparent differences between certain institutions smaller than the corresponding true differences, that is quite unlikely to happen for all ½(34)33 = 561 differences, either individually or in terms of some convenient summary (such as the sum of squares of deviations).

Accordingly, we expect that, over-all but not necessarily individually, true differences in quality of performance between institutions will tend to be somewhat overstated by apparent death rates, under nearly any adjustment. Thus, we strive to reduce such overstatement either to negligibility or as far as we reasonably can, so that any remaining differences are largely true differences.

MEANS OF FURTHER ADJUSTMENT

Standardization--adjustment based directly on differential death rates applicable to identifiable groups of administrations--can take us only so far. We will always have only a limited number of variables, and can expect to expend only a limited amount of effort in adjusting for

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their effects, apparent or real. This being so, what more can we do easily?

If we were able to identify a measurable characteristic of hospitals that (1) is certainly not influenced directly by the average quality of anesthesia and surgery at that hospital and that (2) equally certainly does not directly influence the quality of surgery and anesthesia, but that (3) is clearly associated with the difficulty of the cases brought to operation, we could reasonably eliminate from detailed consideration as much of the hospital-to-hospital differences as could be accounted for by regression on this new variable. (Measures of operative performance and measures of financial strength would be ruled out as likely to be influenced by, or to influence, quality of anesthesia and surgery.) In the language of general statistics, we would be making a regression (or covariance) adjustment with the aid of this variable.

Such an identification would aid us by diversifying our problems, provided that this regression absorbs a reasonably large fraction of apparent institution-to-institution differences. We would then have two phenomena instead of one: (1) Explicit differences between institutions (at least on the average) would be greatly reduced, but would probably continue to deserve some attention; and (2) those differences associated with (i.e., eliminated by the fitting of) the regression would become a specific, broadly occurring phenomenon that both could and should be studied as such. Thus, we would have made important progress in two ways: we would have gained a much better hold on (and a much greater hope of understanding) the differences assembled into (2); and we would have learned that differences due to quality of surgery, anesthesia, and aftercare can only have contributed to the generally smaller differences visible in (1), unless the identified characteristic, which neither influences nor is influenced by performance quality, is somehow correlated with this quality for more complex reasons.

What variable or variables can we consider in the present situation? What measures of over-all riskiness of patients presented do we have? In every case of indirect standardization there is one variable that seems peculiarly appropriate for such purposes. In indirect standardization for any set of strata, we calculate standard deaths = Σ(stratum death rate) (stratum size) and could equally well calculate:

SM = standard death rate
= Σ (stratum death rate) (stratum fraction),

which is the average death rate for an unselected body of cases (drawn from the whole experience) with the distribution over strata of the group of cases studied (here a hospital).

This latter variable clearly measures, about as well as information about the strata considered can, the over-all riskiness of the cases in a given group, here those operated on in a given hospital. It is usually relatively free of influences of quality of anesthesia and surgery, and equally free of influences on this quality. We discuss below the possibility and relevance of influences in the present situation. The use of SM, or of some other measure of an adjustment already made, for regression adjustment of group results is sufficiently general to deserve a name. We shall call it "superstandardization."

Just as standardization can proceed in two ways--"directly" by adjusting the observed death rates, and "indirectly" by adjusting the figures to which the numbers of observed deaths are compared--so too can superstandardization proceed in two ways. We shall here find it convenient to adopt indirect superstandardization, so that we are still comparing the number of deaths actually observed with a reference value--now, we trust, one that is still more suitable.

We must also decide just how we should carry out the regression. On the one hand, it is rather customary so to compute any sort of standardized deaths as to make their sum over all strata equal (or nearly equal) to the corresponding sum of actual deaths. On the other hand, linear regression of the logarithm of SMR on the logarithm of SM seems most likely to give a generally close fit in a wide variety of circumstances. Accordingly, the recommended general procedure is: (1) to do linear regression of log SMR on log SM; (2) to calculate the corresponding number of (indirectly) superstandardized deaths for each stratum, (3) to calculate the common factor by which these should be multiplied to make total superstandardized deaths equal total actual deaths, and (4) to apply this factor to the raw fitted values for each stratum.

How large a fraction of the part of institution-to-institution variability that is associated with differences in intake populations but not dealt with by standardization itself can we expect such a regression adjustment to absorb? One-half? Two-thirds? Three-fourths? Many would think all these numbers too large. We shall consider the consequences of such judgments below.

APPLICABILITY TO THE NATIONAL HALOTHANE STUDY

In the National Halothane Study, why is superstandardization reasonable, and why is it plausible that superstandardization should be effective in reducing apparent differences between hospitals? Without claim or hope of completeness, it is easy to give a few possible reasons.

In the National Halothane Study, the proposed carrier of (additional) regression, SM, is determined by two sorts of information:

(1) over-all death rates, assessed without regard to the institutions in which the deaths occurred, according to categories determined by age group, type of operation, and elective or

emergency character assigned to individual operations; and

(2) the distribution, over these same categories, of all patients brought to operation in particular institutions, as assessed from the randoms.

Because SM is unaffected by transferring deaths in a given category from one institution to another, it is at least a plausible candidate for use in a regression adjustment of standardized death rates for the 34 institutions.

Standardization, according to less-than-adequate strata, frequently leaves an opportunity for further adjustment on the same basis. The simplest case arises when adjustment for a single variable is based on broad groups, as when a continuous variable is dichotomized. Here, the larger the fraction of cases above the cutting point, the higher the center of gravity of these upper-class cases. Consequently, adjustment for percent upper class, although very helpful, still leaves a need for further adjustment in the same direction as the initial adjustment. When we standardize for some but not all of a set of correlated background variables, a somewhat related phenomenon is likely to occur. In the prototype situation, where variable x_1 is stratified on but variable x_2 is not, displacement of both x_1 and x_2 along--or nearly along--a structural regression line common to these two variables will increase x_2 more than would be forecast by the ordinary regression of x_2 on x_1. When differentiation between groups corresponds more or less closely to shifting along a structural regression, standardization of x_1, while allowing for the ordinary regression of x_2 on x_1, will underestimate the correction required to allow for both x_1 and x_2.

The strata used for standardization in the old version of the last section of Chapter IV-6 might have included the age-SLI analysis of the numeric details of "anesthetic risk" in their definition. (Had this been so, better standardization might have ensued.) It is to be expected that the definition of this variable will be at least partly relative to the over-all experience of the hospital concerned. Thus, if two completely equivalent cases are rated, one in a hospital in which the distribution of ages and operation types makes the over-all death rate low, and one in a hospital in which these variables lead to more frequent deaths, it is to be expected that a somewhat higher anesthetic risk will tend to be assigned at the hospital with the lower death rate. As a consequence, the average anesthetic risk in different hospitals would vary less than it should if anesthetic risk were to reflect the same standards in all hospitals. Accordingly, if the details of anesthetic risk did enter, that would cause standardization to underestimate the appropriate adjustments. Fortunately for the simplicity of interpretation of the present analysis, only the emergency-vs.-elective character of anesthetic risk enters into the age-SLI standardization. Although a very small effect on which operations are considered "emergency" is plausible, it is hard to believe that such an effect is in any way important for the present analysis.

Another related effect arises if the decision as to whether marginal patients should be operated on is influenced in a similar direction by the hospital's over-all death-rate experience.

RESULTS OF SUPERSTANDARDIZATION

Let us now turn to the actual situation. The first few columns of Table 1 (in which the hospitals have been arranged in order of the values of SM) give values of both SM and SMR, the standardized mortality ratio, defined by:

$$\text{SMR} = \frac{\text{deaths}}{\text{standard deaths}} = \frac{\text{actual death rate.}}{\text{SM}}$$

The tendency of the SMR to increase as the SM increases is quite obvious in the table. Roughly speaking, the SMR doubles as the SM quadruples.

Consider the regression of the logarithm of the SMR on the logarithm of the SM. Calculation indicates the use of the regression:

$$\log(\text{SMR}) \sim 0.60 \log(\text{SM}) + \text{constant.}$$

When the constant is adjusted to make total superstandard deaths equal total actual deaths (within rounding error), the results shown in the SSMR column are obtained, and hence the indicated number of unbalanced deaths. Other columns show the same figures for the unsuperstandardized SMR. The reduction in unbalanced deaths from 2297 to 1738 consequent on superstandardization is quite striking (these numbers are the averages of the two column totals in Table 1, which disagree because of rounding errors).

(The detailed computations for Table 1 proceeded as follows: Linear regression of $\log_e$SMR on $\log_e$SM gave:

$$\log_e\text{SMR} = 0.60 \log_e\text{SM} + 2.346.$$

Superstandardized mortality ratios, SSMR, were calculated from:

$$\log_e\text{SSMR} = \log_e\text{SMR} - 0.60 \log_e\text{SM} - 2.346,$$

and converted into roughly superstandard (abbreviated "r-superstd") deaths through:

$$\text{r-superstd deaths} = \text{deaths/SSMR.}$$

The sum of all 34 r-superstd deaths was found to be 17364.4, in comparison with the total

TABLE 1.--COMPARISON OF SMR WITH SM, SUPERSTANDARDIZED RESULTS, UNBALANCED DEATHS

Institution	SM	SMR	SSMR	Deaths			Unbalanced deaths			
				Act.	Std	Superstd	Standard		Superstd	
							+	-	+	-
28	0.0076	0.3519	0.6293	19	54	29		35		10
3	0.0093	0.8701	1.3788	201	233	141		32	60	
31	0.0108	1.3433	1.9459	180	135	90	45		90	
17	0.0115	0.8194	1.1431	186	229	158		43	28	
23	0.0115	0.7345	1.0247	83	113	79		30	4	
26	0.0115	0.9011	1.2571	392	438	302		46	90	
6	0.0127	0.8198	1.0715	332	408	299		76	33	
27	0.0129	0.8385	1.0919	296	355	263		59	33	
1	0.0131	0.5643	0.7280	294	524	392		230		98
34	0.0147	1.0778	1.2977	180	168	135	12		45	
22	0.0167	1.2505	1.3946	614	494	427	120		187	
14	0.0170	0.3072	0.3390	141	462	404		321		263
9	0.0179	0.9721	1.0399	976	1010	910		34	66	
12	0.0179	1.1200	1.1981	504	453	408	51		96	
11	0.0187	1.1303	1.1779	555	494	457	61		98	
21	0.0197	0.6352	0.6416	815	1291	1232		476		417
15	0.0201	0.9607	0.9586	586	613	593		27		7
20	0.0201	0.7605	0.7589	727	962	929		235		202
32	0.0207	0.8625	0.8456	276	322	316		46		40
4	0.0210	1.1697	1.1369	717	616	612	101		105	
8	0.0213	0.6948	0.6697	1348	1953	1953		605		605
19	0.0214	1.2398	1.1915	486	395	396	91		90	
10	0.0219	1.2504	1.1852	799	642	654	157		145	
33	0.0242	1.0493	0.9367	681	652	705	29			24
13	0.0248	1.4386	1.2655	246	172	189	74		57	
16	0.0277	1.1611	0.9558	519	450	527	69			8
5	0.0282	1.2802	1.0426	1197	941	1114	256		83	
7	0.0307	1.5486	1.1985	542	352	439	190		103	
18	0.0334	1.1010	0.8101	327	299	391	28			64
30	0.0334	1.5170	1.1162	223	148	194	75		29	
29	0.0336	1.3053	0.9570	171	132	173	39			2
24	0.0384	1.7602	1.1911	1035	591	843	444		192	
2	0.0386	1.6685	1.1256	614	370	529	244		85	
25	0.0434	1.5879	0.9985	578	365	561	213		17	
						Total	+2299	-2295	+1737	-1740

Note: SM is = A-SM, SMR is = A-SMR (in later notation).

actual deaths of 16840. To balance this out, all r-superstd deaths were multiplied by 16840/17364.4 = 0.968. Thus,

superstd deaths = (0.968) (r-superstd deaths).

For institution 28, the actual values were: log SSMR, 0.463; SSMR, 0.6293 (as given); r-superstd deaths, 30.1913; and superstd deaths, 29.23 (rounded to 29).

The standard deaths used in Table 1 are taken from the old version of Table 21 of Chapter IV-6, and involve standardization for age-shock categories. We will henceforth make this explicit by a prefixed "A-," referring to A-SMR, A-SM, A-superstandardized deaths, etc.

This analysis shows a convincingly strong dependence of A-SM on A-SMR and a substantial reduction in the number of unbalanced deaths consequent on changing from standardized to A-superstandardized deaths. The effect is so large that we must be careful to consider all the actions and decisions that could contribute to the values of A-SM.

To change A-SM, we would have to change either the distribution of patients operated on (as to age, sex, and/or operation code), or the distribution of emergency or elective character assigned to their operations.

Accordingly, A-SM is influenced by:

(1) the decisions of specific referring physicians as to when and where their patients should be hospitalized,

(2) decisions at the hospital as to whether or not the patients shall be operated on, and

(3) assignment by the hospital of an emergency or elective character to each operation.

Although we are reasonably clear that (1) and (2) do not directly reflect hospital performance, we dare not be quite so sure of (3). We therefore seek extra security by repeating our superstandardization analysis, using standardization for operations alone--regressing

log O-SMR on log O-SM. Table 2 shows the values of O-SM and O-SMR and various regression coefficients. Again a substantial dependence of log SMR on log SM is clear, although the regression is weaker than for A-SMR on A-SM.

We are now at the following position: Superstandardization could at best be hoped to remove a fraction of that part of the institution-to-institution variance in apparent performance (as measured through the standard mortality ratio, by death rates for crudely equivalent cases) associated with nonperformance variables. It has very substantially reduced the total variance. We have inquired into whether direct effects of institutional differences in quality of anesthesia, surgery, or aftercare could account for the efficacy of superstandardization, and have concluded that they could not, unless an unexpected association were produced in some complex way. Accordingly, the fraction removed by superstandardization must, unless this happens, correspond to nonperformance variables. Because not all nonperformance contributions will be removed, we are led to conclude, with the same caveat, that the portion of institution-to-institution variance in standardized mortality ratios associated with factors other than quality of anesthesia, surgery, and aftercare is greater than the fraction removed by superstandardization, plausibly considerably greater.

There may well be real differences in the quality of performance, as measured by comparative death rates for truly equivalent cases, from one hospital to another within the 34 included in the Study, but we cannot use the data to assert that this must be so. More specifically, we cannot set a lower bound on the variance of performance from institution to institution. However, although the results of superstandardization do estimate a reasonable upper bound for this variance, there are strong reasons to believe that this upper bound, far reduced as it is below the results of mere standardization, is larger than the variance of performance itself by what is likely to be a quite substantial factor.

TABLE 2.--COMPARISON OF O-SMR WITH O-SM AND OF THE ADDITIONAL REGRESSIONS

Institution	O-SM*	O-SMR	
28	0.477	0.287	$\text{A-SMR} = \frac{\text{deaths}}{\text{A-std deaths}} = \frac{\text{death rate}}{\text{A-SM}}$
26	0.511	1.036	
1	0.523	0.716	
14	0.561	0.472	
6	0.573	0.974	$\sim \text{constant}(\text{A-SM})^{0.60}$
31	0.581	1.261	
3	0.598	0.688	
23	0.663	0.651	
27	0.708	0.780	
34	0.719	1.122	$\text{O-SMR} = \frac{\text{deaths}}{\text{O-std deaths}} = \frac{\text{death rate}}{\text{O-SM}}$
22	0.770	1.301	
20	0.800	0.778	
15	0.805	1.223	
17	0.860	0.557	$\sim \text{constant}(\text{O-SM})^{0.41}$
9	0.998	0.897	
21	1.015	0.627	
12	1.045	0.976	
7	1.046	2.309	
32	1.070	0.845	$\text{A-SMR} \sim \text{constant}(\text{O-SM})^{0.38}(\text{A-SM})^{0.25}$
4	1.086	1.149	
5	1.143	1.620	$= \text{constant}(\text{O-SM})^{0.63}(\text{A-SM/O-SM})^{-0.13}$
19	1.203	1.121	
11	1.212	0.887	is equivalent to
10	1.247	1.115	
2	1.271	2.577	$\text{O-SMR} \sim \text{constant}(\text{O-SM})^{-0.62}(\text{A-SM})^{1.25}$
33	1.272	1.291	
8	1.302	0.577	$= \text{constant}(\text{O-SM})^{0.63}(\text{A-SM/O-SM})^{0.87}$
25	1.442	2.413	
16	1.512	1.086	
18	1.685	1.109	
13	1.854	0.979	
29	1.982	1.121	
24	2.331	1.477	
30	2.752	0.935	

*These entries differ from O-SM by a multiplicative constant (the same for all).

THE VARIABILITY OF "UNBALANCED DEATHS"

Let us turn to the question of the actual and estimated variability of:

unbalanced deaths
= actual deaths - superstandard deaths.

It is easy to isolate three major contributions to the variance of each such value, namely:

(1) the variance in actual deaths;

(2) the variance in standard deaths, due to the calculation of estimated exposed from sample results (the randoms), as amplified or diminished by the effects of superstandardization; and

(3) uncertainties in the fit of the coefficients involved in the superstandardization.

The formulas of Appendix 1 to Chapter IV-6 indicate a means of calculating reasonable values for the variances. If Poisson variability applied, we would have:

$$\text{variance}\{\text{deaths}\} \sim \text{deaths, and}$$

$$\text{variance}\{\text{standard deaths}\} \sim Q \cdot \text{standard deaths,}$$

where Q has to be calculated as discussed in Appendix 3.

The corresponding formulas for logarithms (to the base e) are:

$$\text{variance}\{\log_e \text{deaths}\} \sim \frac{1}{\text{deaths}} \text{ and}$$

$$\text{variance}\{\log_e \text{superstandard deaths}\}$$

$$\sim (1.60)^2 \text{variance}\{\log_e \text{standard deaths}\}$$

$$\sim \frac{2.56\,Q}{\text{standard deaths}},$$

where 1.60 = 1 + 0.60, the 0.60 being the regression coefficient, and where we neglect, for the moment, contributions from the variance of the superstandardizing regression coefficient. Because

$\log_e$SSMR
$= \log_e$deaths - $\log_e$superstandard deaths,

we have:

$$\text{variance}\{\log_e \text{SSMR}\} \sim \frac{1}{\text{deaths}} + \frac{2.56\,Q}{\text{standard deaths}}$$

$$= \frac{1 + 2.56(\text{A-SMR})Q}{\text{deaths}}.$$

When we allow for the over-Poisson variation also assessed in Appendix 1, and for the uncertainties due to fitting (in the superstandardizing regression) three constants to 34 data points, it is reasonable to accept

$$\frac{1.1 + 1.54(2.56)\,(\text{A-SMR})Q}{\text{deaths}} = \frac{1.1 + 3.94(\text{A-SMR})Q}{\text{deaths}}$$

as an estimated variance for $\log_e$SSMR.

The best available set of Q's correspond to a closely related but somewhat different basis of standardization. Their use may affect comparisons for individual institutions appreciably, but the over-all picture should not be disturbed by such borrowing.

Having considered regression on both log A-SM and log O-SM separately, it is natural to consider joint regression on both together. Because

log O-SM + log O-SMR = log A-SM + log A-SMR

(both sides being equal to the actual death rate), the residuals after regression of either O-SMR or A-SMR on both O-SM and A-SM will be the same, as will the corresponding numbers of superstandardized deaths. We will use "AO-" to designate such results of joint superstandardization.

The results of AO-superstandardization are set forth in Table 3 with the results of the variability calculations. The ratios of log AO-SSMR to its standard error are obviously too large to be entirely accounted for by sampling fluctuations. The mean square of this ratio is 3.86, in comparison with the 1.0 anticipated for pure sampling fluctuations. The corresponding ratios for $\log_e$SMR are noticeably larger, with a mean square of 7.00. The reduction of excess variability by superstandardization thus appears to be about (7.00 - 3.86)/(7.00 - 1.0) = 52 percent.

Study of the 34 ratios via modified probability plots indicates that three of the $\log_e$AO-SSMR values, those for institutions 14, 8, and 21, are out of line with the other 31, which appear like a sample from a normal (i.e., Gaussian) distribution. A similar analysis for $\log_e$SMR shows that the same three institutions provide three of the lowest five values of "(ratio*)." Omitting those three institutions, the mean square ratios become 2.12 for log AO-SSMR and 5.31 for log A-SMR, corresponding to a reduction of about (5.31 - 2.12)/(5.31 - 0.8) = 71 percent. (An analysis based on the modified probability plot and insensitive to both outliers and long tails yields a reduction of 74 percent in "central variance.")

If we believe that the fraction of the variance associated with quality-unrelated variables that

TABLE 3.--ASSESSMENT OF INSTITUTIONAL VARIABILITY IN COMPARISON WITH SAMPLING VARIABILITY

Institution	AO-SSMR	$\log_e$AO-SSMR	Ster*	Ratio	A-SMR	$\log_e$A-SMR	(Ratio*)
1	0.799	-0.224	0.133	-1.68	0.564	-0.573	-4.30
2	1.296	0.259	0.112	2.30	1.67	0.513	4.56
3	1.280	0.247	0.156	1.58	0.871	-0.138	-0.88
4	1.122	0.115	0.135	0.86	1.17	0.151	1.12
5	1.118	0.112	0.121	0.92	1.28	0.247	2.04
6	1.132	0.124	0.150	0.83	0.819	-0.200	-1.34
7	1.370	0.315	0.130	2.42	1.55	0.438	3.37
8	0.620	-0.478	0.112	-4.28	0.695	-0.364	-3.26
9	1.001	0.001	0.137	0.01	0.972	-0.028	-0.21
10	1.126	0.119	0.120	0.99	1.25	0.223	1.86
11	1.070	0.068	0.136	0.50	1.13	0.122	0.90
12	1.134	0.126	0.135	0.94	1.12	0.113	0.84
13	1.083	0.079	0.126	0.63	1.44	0.365	2.90
14	0.397	-0.924	0.155**	-5.97	0.307	1.181	-7.63
15	1.041	0.040	0.136	0.29	0.960	-0.041	-0.30
16	0.916	-0.088	0.124	-0.71	1.16	0.148	1.19
17	0.996	-0.004	0.167	-0.02	0.819	-0.200	-1.20
18	0.796	-0.228	0.125	-1.83	1.10	0.095	0.76
19	1.138	0.129	0.151	0.85	1.24	0.215	1.42
20	0.826	-0.191	0.130	-1.47	0.760	-0.274	-2.12
21	0.634	-0.456	0.134	-3.41	0.635	-0.454	-3.39
22	1.443	0.367	0.128	2.87	1.25	0.223	1.74
23	0.984	-0.016	0.199	-0.08	0.734	-0.309	-1.55
24	1.089	0.079	0.102	0.78	1.76	0.565	5.56
25	1.142	0.133	0.119	1.12	1.59	0.464	3.91
26	1.334	0.288	0.163	1.77	0.902	-0.103	-0.63
27	1.067	0.065	0.153	0.42	0.839	-0.176	-1.15
28	0.594	-0.520	0.290	-1.79	0.353	-1.041	-3.58
29	0.890	-0.116	0.157	-0.74	1.31	0.270	1.72
30	0.915	-0.088	0.140	-0.63	1.52	0.419	2.99
31	1.918	0.651	0.168	3.88	1.34	0.293	1.75
32	0.834	-0.181	0.143	-1.27	0.862	-0.149	-1.04
33	0.915	0.089	0.136	0.66	1.05	0.049	0.36
34	1.321	0.278	0.157	1.77	1.08	0.077	0.49

Ster* = estimated standard error of $\log_e$AO-SSMR.
(Ratio*) = $\log_e$A-SMR/Ster (calculated for comparison with ratio only).
**Arbitrary Q-value of 2.00 assigned.

is likely to be absorbed by superstandardization is no more than one-half, two-thirds, or three-fourths, we are then led to the following judgment bounds on the fraction of variance in log SMR that may be associated with institutional variation in quality of performance:

(superstandardization reduction)	less than one-half recovery	less than two-thirds recovery	less than three-fourths recovery
(52 percent)	(impossible)	≤22 percent	≤31 percent
(71 percent)	(impossible)	(impossible)	≤5 percent

(Here, for example, if 52 percent is no more than a two-thirds reduction, the whole reduction is no less than 78 percent, hence no more than 22 percent remaining.) The evident conclusion is that only a small fraction of the variation in (unsuperstandardized) institutional standard mortality ratios is likely to be due to institutional differences in performance. (A fraction of 0 percent seems a quite reasonable possibility.)

MORE DETAILED CONSIDERATIONS

The modified-probability-plot examination of logarithmic values of AO-superstandardized mortality rates indicated that three institutions were apparent outliers in the direction of low death rates. The lowest of all, institution 14, had a very distinctive and relevant feature: all cases were classified as "unknown anesthetic risk."

Because these cases could not be divided between the emergency and elective categories, some special treatment must have been required during age-shock standardization.

The second lowest, institution 8, contributed to the Study more than one-third of all the ether administrations in the middle- and high-death-rate operation groups. This fact may well be related to some of the idiosyncratic behavior of ether noted in the course of other analyses.

Neither of these facts leads to firm conclusions; both offer food for thought.

COMPARISON WITH A-SUPERSTANDARDIZATION

The summary effects of double superstandardization (with A-SM and O-SM) are not greatly different from the summary effects of simple superstandardization with A-SM alone. Explicitly:

item	A-superstd	AO-superstd
mean square (all 34)	4.13	3.86
mean square (31 only)	2.19	2.12
"central variability"	2.48	2.43
reduction (all 34)	48 percent	52 percent
reduction (31 only)	69 percent	71 percent
reduction ("central variability")	73 percent	74 percent

However, this small change in over-all numbers is associated with a considerable change in the appearance of the 34 individual SSMR's. The three low values of AO-SSMR are clearly distinguished from the other 31, whereas the three low values of A-SSMR are much less clearly delineated (except for institution 14). In view of the idiosyncrasies (for two of these three) just noted, the analysis indicating these three as distinguished is considered more likely to be informative.

POSSIBLE INTERPRETATIONS OF THESE RESULTS

We have found that, although a few individual differences between institutions appear to remain after superstandardization, the greatest part of institutional differences in standardized mortality ratio (SMR) may be accounted for in terms of regression on one or both forms of standard mortality (A-SM or O-SM). Moreover, the sign of this regression is opposite to that which would arise, in the sort of situation at hand, from fluctuations in estimating the death rates generating the values of SM. The regression effect is large, accounting for most differences between institutions. How could it arise? What approaches might be considered in a later study of its origin and nature?

In view of the very substantial regression of O-SMR on O-SM, neither of whose definitions involves anesthetic risk (physical status), we cannot assign the greater part of this effect to institutional differences in classifying patients on this scale. It would not be unnatural if institutions with a higher fraction of more serious operations, and thus with a more seriously ill patient population, were to classify patients as somewhat lower anesthetic risk than would institutions whose typical patients were less severely ill. Such an effect, if extended to the distinction between elective and emergency operations, would contribute to a positive regression of A-SMR (or O-SMR) on A-SM. Such an effect may well exist, but could not produce the positive regression of O-SMR on O-SM that we have observed.

Differences in judgment as to which patients should be operated on and which are too sick to risk operating on are to be expected. It might well be that institutions in which the patient population is more seriously ill on the average are more likely to operate on equivalent cases. If this effect existed, it would contribute to the observed positive regression. How large such an effect might be must, at this point, be a matter of judgment, but it seems quite unlikely that it would be large enough to account for the size of the observed effect.

In addition to the decision of whether or not to operate, there is an earlier decision by the referring physician as to what institution he will send his patient to. In general, we may expect considerable consensus among referring physicians as to which accessible hospitals are better fitted to deal with more serious cases. In such circumstances, it would be surprising if hospitals receiving a larger fraction of cases scheduled for more serious operations did not also receive, on the average, more difficult cases scheduled for a given operation, even after allowance for age, etc. This would, of course, lead to higher death rates by operation in such institutions. The resulting high SMR would go with the supposedly high SM, and we would again have a positive regression.

A numeric example showing the magnitude of the effects that might be produced in this way may be helpful. Let us suppose an over-all death

rate of 2 percent, with half the deaths coming from more serious cases (whose death rate is 10 percent). For 100,000 cases this requires:

90,000 cases with a 1.11 percent death rate and

10,000 cases with a 10 percent death rate.

If equal numbers of the less serious cases are sent to each of two hospitals, but 85 percent of the more serious are sent to hospital A, the mortality rates become:

$$\frac{500 + 850}{45{,}000 + 8500} = 2.52 \text{ percent and}$$

$$\frac{500 + 150}{45{,}000 + 1500} = 1.40 \text{ percent.}$$

Thus, a ratio approaching 2:1 can arise from what, to the eyes of a layman, seems a not impossible degree of selectivity by referring physicians.

There is a third possibility. The available data in this Study refer to deaths in hospitals. Differences in institutional practice in returning terminal cases to other care (at home or at another institution) could have a noticeable effect on observed mortality rates. This effect could prove to be associated with the value of SM, although both the strength and the direction of such an association are hard to assess.

A fourth possibility deserves mention. Differences in the socioeconomic status of the population served by an institution may be reflected in differences in tendency to delay or avoid entry into hospital. A reasonable consequence could be association of avoidance of minor operations with delay in hospitalization for major ones. If delay corresponded to increased risk of death, this would produce a positive regression of SMR on SM.

Differences in socioeconomic composition might also associate poor general health and nutrition with avoidance of minor operations. This would be a fifth possibility for generating a positive regression coefficient.

Beyond these recognized possibilities, there are undoubtedly other unrecognized ones involving medical phenomena.

In addition, of course, there remain a variety of purely numeric phenomena that might contribute to explaining the observed additional regression on SM. The treatment of age in 10-year classes, for example, in which crude death rates double every decade for the older classes, implies that an appreciable part (perhaps 3 to 10 percent) of the age effect can never be adjusted or standardized for in terms of age classes. Similar phenomena occur for most other variables.

POSSIBILITIES OF FURTHER STUDIES

If it were desired to gather further data that might help to answer the question of which of these recognized possibilities contributes to the observed regression, and how much is thereby contributed, what might be done?

Data relevant to differences in the return of terminal patients to other care could certainly be found, although considerable expenditure of effort and money would probably be necessary. Some light could be thrown on the plausible extent of this effect by studying the termination of stay in hospital according to two competing causes: dismissal and death. More light could be gained by a follow-up study of a substantial sample of patients who underwent operations with relatively high death rates. Investigation of this possibility thus requires considerable effort, but can follow clearly understood approaches.

The second possibility, differential referral, requires a new form of inquiry, and should not be attacked on a large scale without considerable exploratory study and inventive discussion. It seems that some effective approach ought to be possible, but none has yet been identified.

Approximately the same thing can be said about the first, fourth, and fifth possibilities.

THE IMPROVED STANDARDIZATION

We now turn to the improved standardization discussed in the current version of the last two sections of Chapter IV-6. Three standardizations based on cell aggregation of the cross-classification of age, risk (physical status), and operation are relevant here, covering middle-death-rate operations, high-death-rate operations, and middle- and high-death-rate operations combined.

Because of a change in interest and understanding, no such standardization was made for all operations. Thus, direct comparison with results of the original (age-SLI) standardization is not possible. However, comparison of the earlier results for "All" with the newer results for middle- and high-death-rate groups should not be too seriously distorted for our purposes, inasmuch as the low-death-rate operations provide very few deaths and very few standard deaths.

The apparent regression coefficients found for the three analyses were:

Middle:	+0.15
High:	-0.35
Middle-and-high:	+0.07

These are greatly reduced from the +0.60 for the old standardization. Indeed, if we had not had

experience with the old standardization, we would probably pay little attention to such regression coefficients.

COMPARISON OF RESULTS

Table 4 presents various standardized and superstandardized mortality ratios by institution. It is clear that there have been substantial changes, particularly in SMR, in passing from the old standardization (for all operations) to the new standardization (for middle- and high-death-rate operations).

Table 5 presents the sums of squared differences between one mortality ratio based on the old standardization and one mortality ratio based on the new standardization, which is accepted to be better. Whichever new standardized mortality ratio we chose as a reference, it is clear that superstandardizing the old analysis brought it closer to the best values now available.

The individual adjustments made by superstandardization are not all in what would appear to be the right direction, but we would, of course, be quite surprised if they were. As far as the range of values is concerned, Table 6 shows the three lowest and three highest mortality ratios for each of the four types of standardization. Again there is a tendency to better agreement between old superstandardization and either new result.

TABLE 4.--COMPARISON OF VARIOUS STANDARDIZED (SMR) AND SUPERSTANDARDIZED (SSMR) MORTALITY RATIOS

Inst.	New SMR (M+H)	Old SMR (All)	Old SSMR (All)	New SSMR (M+H)	New SSMR (MID)	New SSMR (HI)
28	0.59	0.35	0.63	0.64	0.85	0.30
14	0.60	0.31	0.34	0.62	0.61	0.57
30	0.73	1.52	1.12	0.67	0.65	0.85
8	0.74	0.70	0.67	0.74	0.71	0.81
23	0.74	0.73	1.02	0.76	0.56	1.00
21	0.77	0.64	0.64	0.77	0.78	0.68
33	0.78	1.05	0.94	0.75	0.74	0.83
11	0.78	1.13	1.18	0.76	0.68	0.93
32	0.80	0.86	0.85	0.80	0.76	0.84
1	0.80	0.56	0.73	0.84	0.78	1.02
18	0.84	1.10	0.81	0.81	0.77	0.93
9	0.84	0.97	1.04	0.83	0.74	1.00
17	0.84	0.82	1.17	0.89	0.96	0.81
3	0.88	0.87	1.38	0.92	0.93	0.88
10	0.91	1.25	1.19	0.88	1.23	0.62
6	0.96	0.82	1.07	1.00	0.94	1.11
20	0.97	0.76	0.76	0.98	1.03	0.84
4	1.04	1.17	1.14	1.02	1.11	0.96
26	1.04	0.90	1.26	1.08	1.00	1.45
27	1.06	0.84	1.09	1.11	1.03	1.17
29	1.06	1.31	0.96	1.02	0.79	1.44
19	1.13	1.24	1.19	1.13	1.07	1.28
16	1.14	1.16	0.96	1.11	1.31	0.99
15	1.14	0.96	0.96	1.14	1.01	1.30
2	1.18	1.67	1.13	1.09	1.13	1.13
22	1.20	1.25	1.39	1.21	1.13	1.49
12	1.26	1.12	1.20	1.27	1.17	1.29
34	1.29	1.08	1.30	1.37	1.32	1.67
25	1.31	1.59	1.00	1.22	1.18	1.35
7	1.47	1.55	1.20	1.41	1.50	1.50
24	1.49	1.76	1.19	1.42	1.34	1.63
5	1.52	1.28	1.04	1.50	1.52	1.47
13	1.77	1.44	1.27	1.80	1.51	1.84
31	1.98	1.34	1.95	2.09	1.93	1.94

TABLE 5.--SUMS OF SQUARES OF DIFFERENCES BETWEEN MORTALITY RATIOS BASED ON OLD AND NEW STANDARDIZATIONS

	Old SMR (All)	Old SSMR (All)
New SMR (M + H)	2.4893	1.9499
New SSMR (M + H)	3.2759	1.8711

TABLE 6.--COMPARISON OF THREE LOWEST AND THREE HIGHEST MORTALITY RATIOS

	Three lowest	Three highest
Old SMR (All)	0.31, 0.35, 0.56	1.55, 1.59, 1.76
Old SSMR (All)	0.34, 0.63, 0.64	1.38, 1.39, 1.95
New SMR (M + H)	0.59, 0.60, 0.73	1.52, 1.77, 1.98
New SSMR (M + H)	0.62, 0.64, 0.67	1.50, 1.80, 2.09

BEHAVIOR OF THE MIDDLE-DEATH-RATE GROUP

The most positive regression coefficient is for the middle-death-rate operations. In judging its significance, we need to take account of the fact that log SMR and log SM are subject to correlated sampling fluctuations, so that the natural null-hypothesis value of this regression coefficient is negative, rather than zero. The analysis of Appendixes 4, 5, and 6 to Chapter IV-6 indicates that the negative value for this particular instance is about -0.06.* Accordingly, because the estimated standard error of our regression coefficient is about 0.11, the proper t-ratio is

$$\frac{0.15 - (-0.06)}{0.11} = 1.9,$$

which is significant at a one-sided 5 percent point, rather than

$$\frac{0.15 - (0.00)}{0.11} = 1.4.$$

*See note to Table 2 of Appendix 6 to Chapter IV-6.

OVER-ALL CONCLUSIONS

In discussing the results of the super-standardization based on the old standardization, we concluded that it was reasonable to believe either that better standardization (involving among other things allowance for unmeasured variables) would remove the apparent differences among institutions, or that it would not. Do we now have cause to alter that view?

Table 7, which shows the ratios of highest to lowest and of second-highest to second-lowest for mortality ratios obtained by various standardizations indicates one set of reasons. The new standardization has reduced the highest:lowest ratio from 5.8 (it started at 25.4) to 3.4. Further improvement in standardization might, but need not, reduce this ratio still further. A reduction to, say, 2.0 seems not out of the question. Because a ratio of 1.8 would be expected by chance, it would not require a tremendous further improvement to make the observed ratio quite consistent with the results expected by chance.

However, the large increase in the mortality ratio for institution 31 consequent on super-standardizing the old analysis leads to an old SSMR that agrees quite well with both the new SMR and the new SSMR. One would be inclined to believe that mortality rates in institution 31 are indeed somewhat higher than for other institutions.

Concerning individual institutions, it may help to compare the extreme $(D-\hat{D})/\sigma$ values for the two standardizations. This is done in Table 8. The first thing that strikes the eye is the tremendous reduction in these ratios consequent on using a better standardization. The next thing noticed is the striking behavior of institution 30, which migrates from a critical ratio of +6.0 to one of -3.4. With as weak a degree of association as this between the results of a standardization once thought good enough to use and the results of the present choice, it is hard to be very sure about present results for individual institutions.

Both standardizations were, however, effective in important ways, showing that true institutional differences were much smaller than those among unadjusted death rates, properly discouraging excessive excitement about institutional differences, but preserving an active interest in their cautious exploration.

In summary, then, both views of the eventual results of careful study of institutional differences--no real differences, or small real differences--remain reasonable.

TABLE 7.--HIGHEST AND LOWEST MORTALITY RATIOS AT VARIOUS STAGES OF STANDARDIZATION (INSTITUTION NUMBERS IN PARENTHESES)

	Observed	Operations	Age-SLI*		Age-risk-operation*	
	IV-2, Table 5	IV-2, Table 5	IV-6, App. 2, Table 1		IV-6, App. 2, Table 4	
Mortality ratios						
Highest	3.480(25)	2.577(2)	1.760(24)	[1.946(31)]	1.976(31)	[2.085(31)]
2nd-highest	3.443(24)	2.413(25)	1.668(2)	[1.395(22)]	1.770(13)	[1.806(13)]
2nd-lowest	0.265(14)	0.472(14)	0.352(28)	[0.625(28)]	0.596(14)	[0.644(23)]
Lowest	0.137(28)	0.287(28)	0.307(14)	[0.339(14)]	0.588(28)	[0.619(14)]
Ratios of mortality ratios						
Highest:lowest	25.4	9.0	5.7	[5.7]	3.4	[3.4]
2nd-highest:2nd-lowest	13.0	5.1	4.8	[2.2]	3.0	[2.8]
Expected by chance**						
Highest:lowest				[1.8]		[1.8]
2nd-highest:2nd-lowest				[1.6]		[1.6]

*Superstandardized values in brackets. Values for age-risk-operation standardization are for middle- and high-death-rate groups of operations combined.

**Based on mean values of "ster" for all 34 institutions (probably leads to over-small values) and mean ranges of 4.189σ (full range) and 3.353σ (1st quasirange) for n = 34.

TABLE 8.--EXTREME VALUES OF $(D-\hat{D})/\sigma$ COMPARED (INSTITUTION NUMBERS IN PARENTHESES)

	Old standardization (original version of Table 21 of Chapter IV-6)	New standardization (current version of Table 21 of Chapter IV-6)
Positive extremes	+12.3(24*)	+6.2(24*)
	+8.9(2)	+5.9(13)
	+7.6(25*)	+5.6(5*)
	+6.4(7*)	+5.3(31)
	+6.0(30**)	+4.4(7*)
	+5.3(5*)	+3.6(25*)
Negative extremes	-14.4(14*)	-3.6(14*)
	-7.0(1)	-3.4(8*)
	-6.4(8*)	-3.4(30**)
	-6.0(21*)	-2.7(11)
	-4.2(20)	-2.6(21*)
	-3.0(6)	-2.3(33)

*Repeating at same extreme.
**Repeating at opposite extreme.

APPENDIX 3 TO CHAPTER IV-6

THE VARIABILITY OF THE DIFFERENCE BETWEEN DEATHS AND STANDARDIZED DEATHS

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The two kinds of signed rank analyses in the next-to-last section of Chapter IV-6 are aimed at assessing the statistical significance of the 10 possible agent contrasts, giving more weight to intra-institutional contrasts that (1) are larger or (2) have smaller standard errors. It would be desirable simultaneously to take both these properties of an intra-institutional agent contrast into account; it would further be desirable to give numeric estimates of suitably weighted average contrasts. This appendix exhibits a method developed to meet these two purposes and displays the resulting figures.

Consider a pair of anesthetics α and β. Let j index institution. Define $d_j^{(\alpha,\beta)}$, the difference in the jth institution between the two indirectly standardized mortality ratios, i.e.,

$$d_j^{(\alpha,\beta)} = \log(\mathrm{ISMR}(\alpha))_j - \log(\mathrm{ISMR}(\beta))_j .$$

For convenience now drop α and β from the notation.

We regard d_j as an estimate of a parameter Δ, which is the expected value over institutions of the difference of the logarithms of the indirectly standardized mortality ratios for the two anesthetics. The argument in Appendix 1 to Chapter IV-6 enables calculation of the variance of d_j due to Poisson variation in the deaths and randoms. We denote this variance of σ_j^2. Least squares theory suggests the estimate:

$$\tilde{\Delta} = \sum_j w_j d_j ,$$

where

$$w_j = \frac{1/\sigma_j^2}{\Sigma 1/\sigma_j^2} .$$

We do not choose to use the estimate $\tilde{\Delta}$ because it proceeds from a model that postulates no source of variation in the d_j other than intra-institutional uncertainty. It is plausible that, if no variation of this kind were present at all (e.g., owing to "infinitely large" samples), there would still be variation in the values of the d_j from one institution to another. So we consider the model:

$$d_j = \Delta + \epsilon_j + \delta_j ,$$

where ϵ_j is a fluctuation associated with peculiarities at institution j and δ_j is the intra-institutional Poisson-induced fluctuation in that institution. We further postulate that:

$$\mathrm{Var}\,(\epsilon_j) = \sigma_0^2 \quad \text{and}$$

$$\mathrm{Var}\,(\delta_j) = \sigma_j^2 ,$$

and that all the ϵ_j and δ_j are uncorrelated. Finally, and reluctantly, we suppose the ϵ_j and δ_j to be normally distributed. These assumptions yield the likelihood function:

$$L = c \prod_j (\sigma_0^2 + \sigma_j^2)^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\frac{(d_j - \Delta)^2}{\sigma_0^2 + \sigma_j^2}\right\}.$$

Differentiating $\log L = \mathcal{L}$ with respect to the unknown parameters σ_0^2 and Δ, we obtain the equations:

$$\frac{\partial \mathcal{L}}{\partial \sigma_0^2} = 0 = -\tfrac{1}{2}\sum \frac{1}{\sigma_0^2+\sigma_j^2} + \tfrac{1}{2}\sum \frac{(d_j - \Delta)^2}{(\sigma_0^2+\sigma_j^2)^2} = Q \quad \text{and} \qquad (1)$$

$$\frac{\partial \mathcal{L}}{\partial \Delta} = 0 = \sum_j \frac{(d_j - \Delta)}{\sigma_0^2 + \sigma_j^2} \qquad (2)$$

For given values of the d_j and σ_j^2, these equations are readily solved, iteratively, by trying a value of σ_0^2 that yields a value of Δ in Eq. 2, and then putting both that Δ and σ_0^2 into the expression Q. If that quantity is negative, a smaller value of σ_0^2 is tried next. By successively dividing the intervals where Q is positive and negative, the root $\hat{\sigma}_0^2$ is quickly found, and with it the solution $\hat{\Delta}$. We may take $\hat{\Delta}$ to be approximately normally distributed. Its standard error is estimated in the ordinary way as:

$$\widehat{\mathrm{s.e.}}(\hat{\Delta}) = \frac{1}{\sqrt{\Sigma \frac{1}{\sigma_0^2 + \sigma_j^2}}} .$$

The estimates $\hat{\sigma}_0^2$, $\hat{\Delta}$, and $\widehat{s.e.}(\hat{\Delta})$ were computed for those 28 of the 34 institutions where d_j and σ_j^2 were defined for all anesthetic pairs.

TABLE 1

A. Values of $\hat{\Delta}$ for all anesthetic pairs (middle-death-rate operations)(Figures in parentheses correspond to all-institution ISMR's from Table 12 of Chapter IV-6)[1]

	N-B	C	E	O
H	0.088	-0.202*	-0.319	-0.224*
	(-0.009)	(-0.299)	(0.113)	(-0.220)
N-B		-0.271*	-0.380*	-0.280*
		(-0.290)	(0.122)	(-0.211)
C			-0.096	0.019
			(0.412)	(0.088)
E				0.079
				(0.333)

B. Values of $\widehat{s.e.}(\hat{\Delta})$

	N-B	C	E	O
H	0.091	0.063	0.167	0.082
N-B		0.099	0.177	0.098
C			0.185	0.122
E				0.149

[1] Each figure is positive if the value of log (ISMR) for the row anesthetic was greater than that for the column anesthetic.

Table 1 shows in part A the value of $\hat{\Delta}$. Each value of $\hat{\Delta}$ has beneath it a figure in parentheses, which is $\log(\text{ISMR}_{\text{Row}}) - \log(\text{ISMR}_{\text{Col}})$ computed from the bottom row of Table 12 of Chapter IV-6. It is notable that the present analysis shows ether as less favorable in comparison with each of the other agents than do the figures in Table 12 of Chapter IV-6. This is similar to what happened with the two signed rank analyses, where ether compared adversely with halothane, nitrous oxide-barbiturate, and cyclopropane in contrast to the showing in Table 12. Part B of Table 1 exhibits the estimated standard errors of the values of $\hat{\Delta}$ in part A. Where the magnitude of $\hat{\Delta}$ exceeds twice $\widehat{s.e.}(\hat{\Delta})$, it is starred in part A.

Table 2 displays the estimated values of σ_0^2 for the various pairs of anesthetics. It is notable that all the largest values are associated with ether. It is also notable that for the halothane-cyclopropane comparison σ_0^2 is estimated as zero (a negative value would be necessary to satisfy Eqs. 1 and 2). These facts indicate the instability of ether comparisons from one institution to another, and the stability of the halothane-cyclopropane contrast. Both of these are probably reflections of usage patterns.

TABLE 2.--VALUES OF $\hat{\sigma}_0^2$ FOR ALL ANESTHETIC PAIRS

	N-B	C	E	O
H	0.100	0	0.436	0.058
N-B		0.104	0.495	0.096
C			0.558	0.248
E				0.281

APPENDIX 4 TO CHAPTER IV-6

SHOULD WE SUPERSTANDARDIZE AGENT COMPARISONS?

GENERAL CONSIDERATIONS AND APPARENT CONCLUSIONS

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Appendix 2 to Chapter IV-6 introduced the idea of superstandardization, regression adjustment beyond ordinary standardization of death rates, as a general tool, and as a specific means of improving the basis for comparing one hospital with another. Such objective checks as we were able to make in that appendix indicated that superstandardization was efficacious. Once we recognize superstandardization as a routine tool, it is natural to ask why it should or should not be applied to the comparison of anesthetic agents. It is the purpose of this appendix to explore the possibilities of that application, developing specific techniques to the extent necessary.

The general pattern of our discussion is to consider first what effect the sort of superstandardization thought to be appropriate for institutional comparisons, here called "complete superstandardization," has on agent comparisons, and why we should probably not adopt that approach for agent comparisons. Then we turn to the question of less violent adjustment: how we might estimate how much adjustment to make, and what the consequences of an apparently reasonable adjustment prove to be. We shall conclude by indicating considerable changes in earlier results.

As did the present versions of the last two sections of Chapter IV-6, this appendix developed relatively suddenly at a very late stage in the preparation of the report. As a result, it has not had the benefit of either continuing thought or interstatistician discussion to a degree comparable with many other parts of the report. Moreover, many of the issues that it raises are at a deeper level than seems reachable with the specific sorts of data gathered in this Study. Accordingly, both its techniques and its conclusions are good objects for further inquiry.

COMPLETE SUPERSTANDARDIZATION

The simplest approach would take five values of standardized mortality rates for the five anesthetic agents and superstandardize these values, calculating corresponding standard mortalities by dividing crude death rates by standardized mortality ratios. (The same thing can be done to otherwise adjusted values.) The adjustments thus made in the standardized mortality ratios tend to set a practical upper bound on the adjustments appropriate to reasonable forms of incomplete superstandardization. Accordingly, we look first at them and their consequences, as a preliminary to asking whether they are themselves appropriate as a guide to whether any reasonable adjustment of this sort could make meaningful changes in the results of our other analyses.

The results of such computations for high- and low-death-rate operations and for all operations combined are set out in Table 1. The effect of even complete superstandardization on the high- and low-death-rate groups is quite small, amounting, when we consider median results, to:

	high					low				
	H	N-B	C	E	O	H	N-B	C	E	O
std:	8.4	9.2	11.2	8.3	10.8	0.23	0.16	0.26	0.18	0.33
superstd:	8.5	9.1	11.2	8.7	10.4	0.24	0.17	0.26	0.17	0.32

*Prepared in part in connection with research at Princeton University sponsored by the Army Research Office (Durham).

TABLE 1.--STANDARDIZED (OR OTHERWISE ADJUSTED) AND COMPLETELY SUPERSTANDARDIZED DEATH RATES BY AGENT FOR HIGH-DEATH-RATE, LOW-DEATH-RATE, AND ALL OPERATIONS

Group	Source table*	Standardized death rates, %					Regr. Coeff**	Superstandardized death rates***				
		H	N-B	C	E	O		H	N-B	C	E	O
High-death-rate operations	IV-8,3 } IV-5,1 }	8.44	9.14	10.97	8.11	10.79	+0.28	8.59	9.13	11.22	9.23	10.35
	IV-5,3	8.54	9.23	12.58	8.30	10.84	-0.08	8.13	9.06	11.37	8.64	10.31
	IV-5,5	8.39	9.03	11.66	9.88	10.85	-0.15	8.54	9.32	11.51	9.31	11.11
	IV-6,1	8.27	9.31	11.16	8.19	10.60	+0.20	8.50	9.36	12.40	8.14	10.97
	IV-6,4	8.62	9.20	11.18	9.08	10.44	+0.05	8.30	8.76	11.21	8.70	10.44
	(Median of 5)	(8.44)	(9.20)	(11.18)	(8.30)	(10.79)	(-0.05)	(8.50)	(9.13)	(11.37)	(8.70)	(10.44)
Low-death-rate operations	IV-8,3 } IV-5,1 }	0.25	0.16	0.25	0.18	0.33	-0.19	0.255	0.168	0.254	0.169	0.323
	IV-5,3	0.23	0.16	0.26	0.18	0.34	-0.29	0.243	0.172	0.262	0.164	0.326
	IV-5,5	0.228	0.187	0.271	0.166	0.324	+0.19	0.219	0.183	0.271	0.174	0.329
	IV-6,1	0.23	0.16	0.26	0.18	0.33	-0.22	0.240	0.169	0.261	0.167	0.321
	IV-6,4	0.217	0.185	0.302	0.174	0.304	+0.01	0.216	0.185	0.302	0.174	0.304
	(Median of 5)	(0.23)	(0.16)	(0.26)	(0.18)	(0.33)	(-0.19)	(0.24)	(0.17)	(0.26)	(0.17)	(0.32)
All operations	IV-8,1 } IV-6,6 }	1.95	1.69	2.16	1.56	2.37	+1.16	2.00	1.91	1.75	1.80	2.17
	IV-5,7	1.93	1.72	2.16	1.52	2.33	+1.15	1.98	2.00	1.77	1.72	2.11
	(Median of 2)	(1.94)	(1.70)	(2.16)	(1.54)	(2.35)	(+1.16)	(1.99)	(1.96)	(1.76)	(1.76)	(2.14)

*Chapter, table number.
**Regression of y = log (stdized death rate) on x = log(crude death rate) - log(stdized death rate). Note that y = log SMR + log over-all death rate (for group concerned), and x = log SM + log over-all death rate (for group concerned).
***Log(entry) = y - b(x-$\bar{x}$), where b = regression coefficient and $\bar{x}$ = mean of the 5 x's.

At most, there may be a slight lowering for Other and a slight increase for ether in the high-death-rate group. For all operations combined, the effects are somewhat large, namely (again for medians):

	H	N-B	C	E	O	spread	spread omitting other
std:	1.94	1.70	2.16	1.54	2.35	0.81	0.62
superstd:	1.99	1.96	1.76	1.76	2.14	0.38	0.23

Here we see a considerable pulling together of the results, suggesting a still larger effect of complete superstandardization on the death rates of the middle-death-rate operations.

When we examine Table 2, we see that complete superstandardization of the death rates of the middle-death-rate operations effectively eliminates almost all agent-to-agent differences in death rates. Thus, there is no doubt that superstandardization could have meaningful effects on agent-agent comparisons. For the medians of the first five lines we find:

	H	N-B	C	E	O	spread	spread omitting ether
std:	1.95	1.95	2.56	1.81	2.48	0.75	0.61
superstd:	2.19	2.27	2.24	1.85	2.24	0.42	0.08

Here all agents but ether give completely superstandardized death rates of within 0.04 percent of 2.23 percent. Although the median value for ether is 1.85 percent, the completely superstandardized death rates for the two calculations the authors regard as most trustworthy (the robust estimators of Tables 7 and 8 of Chapter IV-4) give values of 2.37 and 2.48 percent. Accordingly, there is little if any evidence to deny (or to confirm) that ether has a completely superstandardized death rate for middle-death-rate operations that is also close to 2.23 percent.

Because the data for the low-death-rate operations are of limited precision, whereas those for the high-death-rate operations involve a large amount of tailoring of specific anesthetics to specific operations, the main comparison of one agent with another must, for many purposes, be the comparison for middle-death-rate operations. Superstandardization could make very large changes in agent comparisons, so we ask: "Is complete superstandardization appropriate in comparing agents? If not, how much superstandardization is appropriate?"

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judgment might well correlate selection of agent with severity of case in such a way that standardized death rates by agent would become highly correlated with the standard mortalities by agent that sum up the riskiness of specific operations on patients of specific age and anesthetic risk. This might well happen, whatever the true relative quality of the various agents and the corresponding appropriate adjustment for regression on log SM.

A situation not far different from the one we actually face would arise if the agents fell into two subgroups such that all agents within a subgroup were approximately the same, in terms of both log SMR and log SM. Inasmuch as simple linear regression always removes one degree of freedom from comparisons, complete superstandardization in such a situtation would lead to almost complete removal of agent differences, whatever the true state of affairs. (In Appendix 2 to Chapter IV-6, by contrast, our task was simplified by the existence of 34 hospitals, a large enough number for the removal of one additional degree of freedom to be nonessential.) We cannot be sure that such things are not going on. Accordingly, we dare not use the naively apparent regression coefficient, and must seek out other ways to assess a more appropriate regression coefficient. (The results of complete superstandardization are not necessarily wrong, but merely subject to serious doubt.)

If we are to estimate such a more appropriate regression coefficient, it seems highly probable that we should turn to assessing a regression coefficient involving some other comparison of differences in log SMR with differences in log SM. At least three possibilities seem natural:

(1) comparison of institution-to-institution differences (combined across agents),

(2) comparison of institution-by-agent interactions, and

(3) comparison of institution-to-institution differences within agents (which, when averaged over agent, turns out to be a combination of the first two comparisons).

HOW SHOULD WE ESTIMATE?

Before turning to the actual calculations, we must prepare for the fact that all the quantities with which we are concerned, including log SM, are measured with error. Thus, apparent and structural regressions will differ, and the actual amounts of error involved will affect our results. We will therefore not be able to borrow overt, apparent regression coefficients. Instead, we must try to estimate so-called structural regression coefficients, in which the effect of more or less inevitable, meaningless fluctuations common to log SM and log SMR has been eliminated or, more realistically, greatly reduced.

For a long time, nearly all discussions of simple linear regression between two variables considered only two components for each variable, one rigorously following the linear regression, the other consisting of independent errors and fluctuations. Most discussions, indeed, restricted the possibility of the second component to only the y-variable, so that "regression with both variables subject to error" was often regarded as a recondite subject. Already in this latter case there are two different regressions of y on x with different interpretations and different areas of usefulness.

If we have observed pairs (x,y) that consist of strictly linearly related values (ξ,η), modified by additive fluctuations $x-\xi$ and $y-\eta$, then the observed variance of x and the covariance of x and y lead to an observed (or apparent) regression coefficient $\hat{c}ov(x,y)/\hat{v}ar\ x$. This is the regression coefficient most appropriate to predicting or approximating a value of y given the corresponding value of x.

There is also the regression coefficient of η on ξ. If we could obtain estimates $\hat{c}ov(\xi,\eta)$ and $\hat{v}ar\ \eta$ of the covariance and variance of these structural variables, their ratio $\hat{c}ov(\xi,\eta)/\hat{v}ar\ \eta$ would estimate the structural regression coefficient of y on x, which is the same as the actual regression coefficient of η on ξ. If, starting from a randomly selected (x,y) pair, we make a change in ξ and observe the corresponding change in x, the best estimate of the corresponding change in y is that based on the structural regression coefficient. This is so because in that situation, the best estimate of the change in ξ is given by the change in x, whereas the average change in y is equal to the change in η. Thus, the regression coefficient of η on ξ is the appropriate regression coefficient to use. Notice that the best estimate of the difference in ξ's is not given by the difference in x's when we are concerned with two randomly selected (x,y) pairs.

Our present situation is complicated in two ways, beyond the usual "error in both variables" situation just described: (1) the relation of η to ξ need not be precisely linear (η has a linear regression on ξ that may take up little or much of the variation, but not all); and (2) the independent fluctuations basic to the definition of ξ and η are not in x and y, but rather in $v = y + x$ and x. These complexities are partially compensated for by the fact that we have more than just pairs (x,y) to work with; indeed, we can estimate (rather crudely) what the fluctuation or sampling variance of x appears to be.

Appendix 5 to Chapter IV-6 treats the mathematical-statistical details involved in obtaining an appropriate estimate for such a structural regression coefficient. The formula reached there is:

$$\text{structural-b} = \frac{\hat{c}ov(\log SMR,\ \log SM) + \hat{\sigma}^2_x}{\hat{v}ar(\log SM) - \hat{\sigma}^2_x},$$

TABLE 2.--STANDARDIZED (OR OTHERWISE ADJUSTED) AND COMPLETELY SUPERSTANDARDIZED DEATH RATES BY AGENT FOR MIDDLE-DEATH-RATE OPERATIONS

Source table*	Standardized death rates, %					Regr. Coeff**	Superstandardized death rates***				
	H	N-B	C	E	O		H	N-B	C	E	O
IV-4,6	1.92	1.99	2.54	1.81	2.41	+0.64	2.13	2.27	2.18	1.85	2.17
IV-4,7	2.01	1.95	2.56	2.17	2.47	+0.53	2.19	2.10	2.21	2.37	2.24
IV-4,8	2.02	1.95	2.55	2.27	2.48	+0.44	2.16	2.06	2.24	2.48	2.28
IV-8,3 } IV-5,1 }	1.93	1.97	2.78	1.77	2.57	+0.99	2.22	2.33	2.34	1.74	2.28
IV-5,1	1.95	1.95	2.79	1.79	2.52	+1.02	2.27	2.29	2.35	1.78	2.23
(Median of 5)	(1.95)	(1.95)	(2.56)	(1.81)	(2.48)	(+0.64)	(2.19)	(2.27)	(2.24)	(1.85)	(2.24)
IV-6,12	1.98	2.00	2.68	1.77	2.52	0.73	2.24	2.30	2.31	1.75	2.28
IV-5,3	1.93	1.97	2.78	1.77	2.57	+0.96	2.25	2.32	2.33	1.76	2.28
	1.95	1.95	2.79	1.79	2.55	+1.09	2.21	2.35	2.27	1.89	2.25
IV-5,5	2.04	1.94	2.75	1.73	2.56	+0.74	2.36	2.18	2.40	1.68	2.33
IV-6,1	1.95	1.96	2.77	1.81	2.55	+1.00	2.26	2.30	2.32	1.81	2.23
	1.92	1.95	2.77	1.84	2.60	+1.15	2.23	2.33	2.25	1.87	2.28
IV-6,4	2.00	2.05	2.61	1.91	2.49	+0.63	2.22	2.32	2.23	1.97	2.24
IV-6,7	2.08	2.04	2.56	1.96	2.49	+0.52	2.30	2.25	2.22	2.03	2.27
	1.95	1.94	2.73	1.81	2.62	+1.04	2.27	2.27	2.23	1.81	2.35
	2.00	2.05	2.61	1.91	2.22	+0.40	2.16	2.24	2.39	1.96	1.99
IV-6,8	2.05	1.99	2.70	1.77	2.54	+0.67	2.34	2.24	2.35	1.74	2.31
	1.98	1.89	2.82	1.69	2.63	+0.93	2.32	2.14	2.44	1.60	2.41
	2.04	1.94	2.75	1.73	2.56	+0.74	2.36	2.18	2.40	1.68	2.33
	2.08	2.02	2.70	1.79	2.56	+0.63	2.36	2.26	2.36	1.77	2.34
	2.01	1.93	2.78	1.66	2.60	+0.70	2.29	2.15	2.48	1.57	2.42
	2.05	1.96	2.74	1.73	2.56	+0.69	2.35	2.20	2.40	1.68	2.34
(Median of 15)	(2.00)	(1.96)	(2.75)	(1.79)	(2.56)	(+0.74)	(2.29)	(2.25)	(2.35)	(1.77)	(2.31)

*Chapter, table number.

**Regression of y = log(stdized death rate) on x = log(crude death rate) - log(stdized death rate). Note that y = log SMR + log over-all death rate (for group concerned), and x = log SM + log over-all death rate (for group concerned).

***Log(entry) = y - b(x-$\bar{x}$), where b = regression coefficient and $\bar{x}$ = mean of the 5 x's.

POSSIBLE DIFFICULTIES IN COMPLETE SUPERSTANDARDIZATION

Once we have chosen the variable on which we are to regress the logarithm of the standardized (or otherwise adjusted) death rate, we have separated the differences among the five agents in two complementary parts: a one-dimensional part corresponding to differences that can be explained (fitted) by regression, and a three-dimensional part that is entirely unaffected by the choice of coefficient in a regression adjustment. Together these parts can describe any instance of the 3 + 1 = 4-dimensional manifold of possible sets of differences among the five agents.

The principal conclusion of the last section may be put thus: For the middle-death-rate operations, the three-dimensional part of the differences among agents contributes essentially nothing to either observed or adjusted differences among agents. Thus, the whole question of agent comparison for the middle-death-rate operations is reduced to: "How much of the one-dimensional part (i.e., of the differences that regression accounts for) should be taken to be real and how much should be taken to be an artifact of the original analysis and removed by an appropriate regression adjustment?"

The basic questions become questions about the numeric values of the regression coefficient to be used in the adjustment. And the concluding questions of the preceding section become: "Are we sure that we should use the regression coefficient based only on the standardized death rates for the five agents (which corresponds to complete superstandardization)? If not, where should we seek a better regression coefficient for this purpose?"

Matters would be simpler if we could answer "yes" to the first question, but it is relatively clear that we dare not. Agents are selected with regard to the clinical pictures presented by individual patients. Anesthesiologic

where

$\hat{c}ov(\log SMR, \log SM)$ = the sample (or estimated) covariance between log SMR and log SM (across whatever comparisons are being borrowed from),

$\hat{v}ar(\log SM)$ = the sample (or estimated) variance of log SM (across the same comparisons), and

$\hat{\theta}_x^2$ = an estimate of the part of the variance of log SM that is wholly unrelated to log SMR (being mainly due to sampling fluctuations).

This formula is easily modified (see Appendix 5) to apply to weighted analyses. In any case, we have to give serious attention to the relation of the numbers that we use for $\hat{\sigma}_x^2$ to the numbers calculated on the assumption that deaths and randoms are subject only to Poisson sampling variability (see Appendix 1 to Chapter IV-6). We have chosen to state our results for two extreme values of the factor

$$\hat{\sigma}_x^2/(\hat{P}oiss\text{-}var \log SM),$$

namely, 1.0 and 1.5 (for whose choice see Appendix 5), thus allowing both mental adjustment to a chosen value of this ratio and clear insight into its importance in affecting the values of structural-b.

RESULTING VALUES OF STRUCTURAL-b

The results of a number of different approaches to the estimation of structural-b are collected for comparison in Table 3 of Appendix 1 to Chapter IV-6. We can hope that these diverse approaches will reach similar results, but we must be prepared for any sort of complexity. All these approaches refer to the middle-death-rate operations and are based on the 15-aggregation-strata standardization used in the last section of Chapter IV-6 and in the later analysis of Appendix 2, the best standardization for which detailed figures are available.

The computation of these results is discussed in detail in Appendix 6 to Chapter IV-6. The one-way analyses involve, respectively: (1) values of log SMR and log SM for institutions (based on pooled results for all agents) and unweighted regression; (2) similar values for institution-agent combinations, regressed separately within each agent (using weights appropriate to that agent), and the estimated structural regression coefficients averaged with equal weight for different agents; and differences, δ log SMR in log SMR and δ log SM in log SM, for a particular pair of agents regressed over institutions (using weights appropriate to that pair), the resulting estimates of structural regression coefficients being averaged with equal weight for different pairs of agents. The two-way analyses are based on a condensation of the 34 institutions and five agents to 15 compound institutions and three compound agents, so chosen as to bring together cells with similar values of log SM and to make the weights appropriate to each of the 15×3 new cells close enough so that unweighted two-way analysis is relatively efficient. Making such a two-way analysis, collecting sums of squares for both log SMR and log SM, as well as sums of cross-products, enables us to calculate structural regression coefficients based on: (1) differences between composite agents (which we discard for varied reasons), (2) differences between composite institutions, or (3) interactions between these two composite variables. The results of the latter two choices are given in Table 3.

Table 3 has two columns and five rows. The columns represent extreme alternatives concerning the actual variability (of logarithms) of standard mortality. (The authors felt, before this table was prepared, that a factor much closer to 1.5 than to 1.0 was likely to be appropriate.) In interpreting the table, we should interpolate between these columns, being guided both by the analyses of Appendix 1 and by the effect of this choice on the consistency of our results from row to row. We would hope that the results for the five rows would be in reasonably close agreement, because it is then that our problems of interpretation are simplest.

When we look at the table we do see reasonable consistency. The three types of one-way analysis give, for a factor of, say, 1.5, estimates of 0.21, 0.18, and 0.16. (A factor of 1.6 would give 0.21, 0.19, and 0.20.) The two types of two-way analysis give, for a factor of 1.2, estimates of 0.28 and 0.31. It would thus be hard to exclude any value between 0.2 and 0.3, and it seems quite reasonable to adopt a value of 0.25. (As in so many other analyses, this is somewhat predicated on omitting ether, which behaves quite distinctively in the within-agent and between-agents analyses based on institutional differences.) Accordingly, we shall shortly trace the consequences of adopting this value for structural β.

WHY MIGHT ADJUSTMENT BE SOUND?

Before beginning to trace these consequences, we ought to ask whether there is any excuse for a superstandardization-like adjustment in connection with agent-to-agent differences. As usual, there are a variety of possible reasons.

As noted in Appendix 2 to Chapter IV-6, we know that any standardization by strata, even one based on 15 aggregation strata, is far from perfect. There will be need for further adjustment

TABLE 3.--COLLECTED ESTIMATES OF STRUCTURAL-b

Source of estimate	$\hat{\beta}^2_x/(\hat{\beta}_{Poiss}$-var log SM) 1.0	1.5
One-way analysis (based on 34 institutions and four or five agents):		
Institution-to-institution differences for all agents combined	0.19	0.21
Institution-to-institution differences within agent		
(Weighted; ether omitted except in parentheses)	0.13(0.10)	0.18(0.15)
Institution-to-institution differences in agent-to-agent differences		
(Weighted; ether omitted except in parentheses)	-0.04(-0.18)	0.16(-0.03)
Two-way analysis (based on 15 compound institutions and three compound agents*):		
Institution-to-institution differences	0.27	0.29
Interactions of institutions and agents	0.20	0.47

*The 15 compound institutions were:17+28+30, 3+27+31+34, 1+6+14+26, 8+13+23, 20+21, 12+19+22+32, 15+16, 4+9, 5+10, 11, 7+29, 24+33, 18, 25, and 2; the three compound agents were: halothane alone, nitrous oxide-barbiturate combined with ether, and cyclopropane combined with Other.

that, under plausible assumptions, will correlate quite highly with the adjustment already made by the use of the strata (i.e., with log SM). Notice, in particular, that we have not yet allowed for the fact that, for low- and middle-death-rate operations, a patient x-ty-9 years old is subject to almost twice the death rate of patient x-ty-1 years old for x = 4, 5, 6, 7, or 8 (and probably for x = 3 or 9, also).

In another direction, many variables not measured in this Study may contribute to the riskiness of operations. To the extent that these unmeasured variables are correlated, among agents, with those that were measured, there is a real possibility (as discussed in Appendix 2) that the effects of the unmeasured variables will be correlated with the effects of the measured variables in such a way as to require superstandardization-like adjustments.

In a third direction, preferential assignment of higher-risk patients to certain agents, whether or not all the variables relevant to the risks were measured in this Study, can produce a need for a superstandardization-like adjustment.

All in all, we find it quite reasonable that further adjustment according to structural $\beta = 0.25$ compensates for real effects whose cancellation is desirable.

FIRM CONSEQUENCES OF STRUCTURAL $\beta = 0.25$

Table 2 gives agent comparisons for a wide variety of analyses. We have selected three of these for careful consideration of the effects of partial superstandardization: the 15-aggregation-strata analysis of Table 12 of Chapter IV-6 and the robust smear-and-sweep analyses of Tables 7 and 8 of Chapter IV-4. All these analyses include careful assessments of significance; all show that differences between certain pairs of agents are significant. Although based on different approaches, the results are rather similar. They are certainly among the most sensitive analyses of significance so far available.

Table 4 shows the effect of adjusting standardized death rates for a structural β of 0.25. The changes are perhaps not strikingly large, but, as we shall soon see, their consequences are substantial. Table 5 shows the more crucial effects of adjustment on the differences in death rates that are our prime concern. We see that agent-to-agent differences are reduced to between two-thirds and one-half of their previous values. If such a reduction were to occur without change in the "error variances" against which these differences are compared (actually or effectively) in significance tests, then most instances of weak, moderate, or quite strong significance would be converted into nonsignificance.

The effect of adjustment for a structural β of 0.25 on "error variance" is far from certain. Either no reduction or a quite substantial reduction is quite possible. The most natural basis for a crude estimate is the reduction in error term in the two-way analysis involving compound institutions and compound agents. Here a reduction of some 25 percent seems to be indicated. This would decrease standard deviations in the ratio $(100 \text{ percent}-25 \text{ percent})^{1/2}/(100 \text{ percent})^{1/2} = 0.866$, corresponding to the change from "ratio" to "ratio*" in Table 5, as far as the ratio of differences to their standard errors is concerned. This still leaves us with reductions in (differences in death rates)/(estimated standard error of same) by factors of three-fifths to four-fifths. What are the consequences of such a reduction?

GUESSED (PLAUSIBLY INFERRED) CONSEQUENCES OF ADJUSTMENT

Our proposed adjustment in "error variance" is itself subject to considerable uncertainty. Moreover, its application to any of the analyses

TABLE 4.--EFFECTS OF ADJUSTMENT FOR A STRUCTURAL β OF 0.25 ON DEATH RATES FROM THREE ANALYSES

Source table*	Standardized death rates, %				
	H	N-B	C	E	O
IV-6,12**	1.98	2.00	2.68	1.77	2.52
IV-4,7	2.01	1.95	2.56	2.17	2.47
IV-4,8	2.02	1.95	2.55	2.27	2.48
(raw***)	(1.727)	(1.709)	(3.401)	(1.855)	(2.988)
	Adjusted death rates, %				
IV-6,12**	2.05	2.08	2.52	1.75	2.42
IV-4,7	2.09	2.03	2.38	2.25	2.36
IV-4,8	2.10	2.03	2.37	2.16	2.37
	Relative standard mortalities				
IV-6,12	1.15	1.17	0.79	0.95	0.84
IV-4,7	1.16	1.14	0.75	1.17	0.83
IV-4,8	1.17	1.14	0.75	1.22	0.83

*Chapter, table number.
**The over-all death rate of middle-death-rate operations, 2.207 (see Table DR-5 of Chapter IV-2), applied to the over-all standard mortality ratios at the foot of Table 12 of Chapter IV-6.
***From Chapter IV-2; for comparison and as used in adjustment.

of the next-to-last section of Chapter IV-6 or the third section of Chapter IV-4 is subject to further question. Accordingly, any conclusions we may attempt to reach about the effect of adjustment on the assessed significance of agent-to-agent differences must be regarded as guesses, or perhaps plausible inferences.

The applications to the analyses of Chapter IV-4 are relatively direct, so that only questions of applicability are important. However, because of the detailed nature of the analyses of Chapter IV-6, applications to these, to which we turn first, are quite indirect and subject to additional questions. Ratio* for these analyses is close to 0.77. Table 14, after selective elimination of ether, reaches a chi-square of 10.2 on three degrees of freedom. Although not justifiable, it is not unreasonable to guess by multiplying this by about $(0.77)^2$, reaching a chi-square of 6.05, corresponding to $p = 0.11$. This is our nearest guess as to what reanalysis might give.

In the rank analyses of Tables 16 and 17 of Chapter IV-6, there are 40 critical ratios derived from paired analyses with the aid of ranks. Some 15 (2+6+3+4) of these are starred as exceeding 2.00 in magnitude. If these critical ratios were to be shrunk in the ratio 0.77 by a reanalysis taking account of a structural β of 0.25, which is not implausible, six (1+2+1+2) of them would still exceed 2.00. In 40 null trials we must find an average of 2 beyond the 5 percent point. Would 6 be strong evidence, where 2 must occur on the average? Even if the occurrences were independent, 6 or more would occur in 1.4 percent of all cases. In the present situation, where there is a large amount of dependence, we could hardly regard 6 as strong evidence of the differences. (If we try to reduce the effects of dependence by going to individual sets of 10 comparisons, we find 1 or 2 observed when 0.5 must occur on the average. The corresponding tail areas are $p = 0.40$ and $p = 0.086$, again far from clear evidence.)

Turning to the robust smear-and-sweep analyses of Tables 7 and 8 of Chapter IV-4, we can guess at the effect on the confidence intervals found there by (1) replacing the standardized differences that determine the centers of the confidence intervals with adjusted differences, and (2) shortening these confidence intervals to 87 percent of their former length. The results are shown in Table 6.

Whereas the original analyses agreed that three agent-to-agent differences in standardized death rate were significant, and that the fourth came

TABLE 5.--EFFECTS OF ADJUSTMENT FOR A STRUCTURAL β OF 0.25 ON DEATH-RATE DIFFERENCES FOR THREE ANALYSES

Source table	Item	Difference in death rates			
		C minus H	O minus H	C minus N-B	O minus N-B
Chapter IV-6, Table 12	Std	0.70%	0.54%	0.68%	0.52%
	Adj	0.47%	0.37%	0.44%	0.34%
	Ratio	0.67	0.69	0.65	0.65
	Ratio*	0.77	0.80	0.75	0.75
Chapter IV-4, Table 7	Std	0.55%	0.46%	0.61%	0.52%
	Adj	0.29%	0.27%	0.35%	0.33%
	Ratio	0.53	0.59	0.57	0.63
	Ratio*	0.61	0.68	0.66	0.73
Chapter IV-4, Table 8	Std	0.53%	0.46%	0.60%	0.53%
	Adj	0.27%	0.27%	0.34%	0.34%
	Ratio	0.51	0.59	0.57	0.64
	Ratio*	0.59	0.68	0.66	0.74

*Ratio adjusted for a possible reduction in error variance of 25 percent associated with adjusting the death rates.

very close to significance, the guessed results for a similar analysis based on adjusted rates are very different. Only one difference barely reaches significance, and that is only one of two analyses. (A further notable aspect is the substantial guessed reduction in the upper limits of the confidence intervals. The averages for the two original analyses are 1.02, 0.78, 1.18, and 1.08 percent. The guessed replacements are 0.70, 0.55, 0.85, and 0.85 percent.)

It is fair to say that our best guess as to the effect of adjustment for a structural β of 0.25 on all three analyses is that it would bring the assessed significance of all differences below the usual levels.

(Some readers may prefer some other value of structural β, larger or smaller than 0.25. The note on Table 6 may help in assessing the consequences.)

WHERE DO WE STAND?

Adjustment for a structural β of 0.25 (which we do not claim to have assessed with high precision, and whose appropriateness is subject to discussion) reduces agent-to-agent differences for the middle-death-rate operations, and seems likely to reduce them below the usual levels of significance, insofar as can be guessed from the computations presented here.

In preparing to summarize the over-all position, it is especially important to recognize that the general agreement of unsuperstandardized agent comparisons, as to order of apparent death rates and their apparent significance, is heartening, because it indicates that different approaches have educed quite similar results from the same data, thus raising our confidence in their common answer to a certain question. If, however, adjustment for an appreciable structural β is appropriate, all these analyses are answering an inappropriate question. Only appropriately adjusted analyses would then be relevant.

A reasonable summary, then, would seem to be as follows, considering that we regard a limited superstandardization-like adjustment as appropriate:

(1) The sizes of the apparent agent-to-agent differences in death rates found for the middle-death-rate operations elsewhere in this report should be reduced to about three-fifths of the values stated, although one cannot be entirely sure of the appropriateness of this reduction. (This leaves cyclopropane and Other with apparent

TABLE 6.--GUESSED EFFECTS OF ADJUSTMENT FOR A STRUCTURAL β OF 0.25 ON THE CONFIDENCE INTERVALS OF THE ANALYSES OF TABLES 7 AND 8 OF CHAPTER IV-4

Source table	Difference	Confidence interval, %	
		Original	Modified (guessed)
Chapter IV-4, Table 7	C minus H	0.03 to 1.06(*)	-0.14 to 0.74
	O minus H	0.10 to 0.82(*)	-0.04 to 0.58
	C minus N-B	0.03 to 1.18(*)	-0.15 to 0.85
	O minus N-B	-0.05 to 1.08	-0.16 to 0.85
Chapter IV-4, Table 8	C minus H	0.09 to 0.98(*)	-0.12 to 0.66
	O minus H	0.17 to 0.74(*)	+0.02 to 0.52(*)
	C minus N-B	0.05 to 1.17(*)	-0.15 to 0.83
	O minus N-B	-0.02 to 1.08	-0.14 to 0.82

Note: A rough idea of the consequences of choosing different structural β's is obtained if we take changes in agent-to-agent differences proportional to structural β. Thus, if we take $\beta = 0.10$, the lower limits of the modified (guessed) confidence intervals above would be, in order: -0.04, +0.04, -0.04, -0.09, +0.01, +0.11, -0.03, and -0.07 percent, so that three of the eight comparisons would prove significant.

death rates for middle-death-rate operations of about 7/6 of those for halothane and nitrous oxide-barbiturate.)

(2) The significance, at the usual levels, of all differences between agents for middle-death-rate operations is subject to question.

(3) Further analyses could throw some light on the situation (as by replacing the guesses of the preceding section with facts), but questions about plausibility of different possible sources for a need for the further adjustments made in this appendix are likely to require a more subtle and comprehensive study for their elucidation.

(4) If the limited superstandardizing adjustment presently considered reasonable proves to be unsound, it is possible either that the results obtained elsewhere should be accepted without adjustment or that larger adjustments than here contemplated would be appropriate.

(5) Although the high-death-rate operations are distinctive enough to require individual consideration, we do need to recall that, in the proportions used during the period of this Study, halothane does appear to show a more favorable death rate than, for example, cyclopropane, whatever superstandardization-like adjustment we may contemplate.

What conclusions concerning the relative safety of, for example, halothane and cyclopropane would be justified if the adjustment reached in this appendix were accepted and the guessed effects on other analyses proved to be correct? There is only one: that the apparent difference in death rates after the use of, for example, halothane and cyclopropane, as applied with much guidance from anesthesiologic judgment, appears to be smaller than might otherwise have been thought, and in fact is no longer statistically significant at the usual levels of significance (although it is rather close to significance). In interpreting these changes, we need to be keenly aware that we are not directly measuring the effect of changing the anesthetic given to a patient, either individually or on some average (a retrospective study cannot do that), but rather are measuring something relevant to this effect but subject to disturbances of unknown size and amount. The discussions of this appendix lead to smaller (and less statistically significant) suggested differences; they do not, however, change the direction of any suggested difference or appreciably reduce the uncertainties about the gap between what is suggested by our analyses and what changing anesthetics would do in practice.

What death-rate evidence is at hand still favors halothane over cyclopropane. The scope of the Study and the delicacy of its analysis still go far beyond anything previously available. The uncertainties in interpretation remain.

APPENDIX 5 TO CHAPTER IV-6

DEVELOPMENT OF CERTAIN FORMULAS

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In this appendix, we develop a number of formulas needed in the considerations of Appendix 4 to Chapter IV-6. These formulas all relate to the regression of log SMR on log SM, where SMR is a ratio of observed deaths to standard deaths and SM is a standard death rate.

THE EFFECT OF ERRORS IN ALL VARIABLES

Let us define v, x, and y as follows:

y = log SMR (or something differing from this by a constant),

x = log SM (or something differing from this by a constant), and

v = log observed death rate (or something differing from this by a constant).

Then

$$v = y + x,$$

and fluctuations due to sampling will affect v and x (not y and x) nearly independently. That will be so because x depends on (1) the distribution of cases brought to operation with the cell or stratum involved, and (2) deaths in all strata or cells, whereas v depends on deaths in only the stratum or cell concerned.

Let, then,

σ_v^2 = contribution to the variance of v from sampling fluctuations,

σ_x^2 = contribution to the variance of x from sampling fluctuations (and from other sources not described by τ_v^2 and γ),

τ_v^2 = contribution to the variance of v from long-run differences in strata or cells, and

γ = rate (regression coefficient) by which these long-run differences in v contribute to x.

Because $y = v - x$, it follows that

$$\text{var } x = \sigma_x^2 + \gamma^2 \tau_v^2,$$

$$\text{cov}(x,v) = \gamma \tau_v^2, \text{ and}$$

$$\text{var } v = \sigma_v^2 + \tau_v^2.$$

Consequently,

$$\text{cov}(y,x) = \text{cov}(v-x,x) = \gamma \tau_v^2 - \gamma^2 \tau_v^2 - \sigma_x^2,$$

and the apparent regression coefficient of y on x is

$$\frac{(\gamma-\gamma^2)\tau_v^2 - \sigma_x^2}{\gamma^2 \tau_v^2 + \sigma_x^2}.$$

Now, if we put $\tau_x^2 = \gamma^2 \tau_v^2$ and $\beta \tau_x^2 = (\gamma-\gamma^2)\tau_v^2$, so that $\beta = (\gamma-\gamma^2)/\gamma^2$, these become:

$\beta \tau_x^2 - \sigma_x^2$ = apparent covariance of y and x,

$\tau_x^2 + \sigma_x^2$ = apparent variance of x, and

$\dfrac{\beta \tau_x^2 - \sigma_x^2}{\tau_x^2 + \sigma_x^2}$ = apparent regression coefficient.

If we had a nearly infinite amount of data for each stratum or cell, the σ_x^2 terms could be neglected, and the apparent regression of y on x would be β. Thus, β is the structural regression of y on x. If σ_x^2 cannot be neglected, but $\hat{\sigma}_x^2$ is a reasonable estimate of it, then an appropriate estimate of β is:

$$\text{structural-b} = \frac{\hat{\text{c}}\text{ov}(y,x) + \hat{\sigma}_x^2}{\hat{\text{v}}\text{ar } x - \hat{\sigma}_x^2},$$

which is worth considering only when $\hat{\text{v}}\text{ar } x - \hat{\sigma}_x^2 > 0$ (by an appreciable fraction of $\hat{\sigma}_x^2$). Notice that,

*Prepared in part in connection with research at Princeton University sponsored by the Army Research Office (Durham).

because a negative value of $\hat{c}ov(y,x)$ can be outweighed by a positive value of $\hat{\delta}^2_x$, structural-b may have the opposite sign to

$$\text{observed regression coefficient} = \frac{\hat{c}ov(y,x)}{\hat{v}ar\ x}.$$

WEIGHTED ANALYSES

When, as is so often the case, the variabilities of the different y differ in a known or estimable way, and when these differences are substantial, unweighted combination of various differences is of little merit, because of low efficiency. In such situations, we wish to take advantage of weighted combinations, which will be helpful (as far as efficiency goes) if the ratios of the weights are even roughly correct.

To deal with the extension of the formula just given to weighted analyses, we need to know a few algebraic-arithmetic facts about the usual expressions arising in a weighted analysis. Let

$$WSS_y = \Sigma w_i (y_i - y_W)^2 \text{ and}$$

$$WSS_x = \Sigma w_i (x_i - x_W)^2,$$

where

$$y_W = \frac{\Sigma w_i y_i}{\Sigma w_i} \text{ and } x_W = \frac{\Sigma w_i x_i}{\Sigma w_i}$$

are the similarly weighted means of the y's and x's. Also, let

$$WSP = \Sigma w_i (y_i - y_W)(x_i - x_W) \text{ and}$$

$$WSV = \Sigma w_i \hat{\delta}^2_{xi},$$

for which the requirement on $\hat{\delta}^2_{xi}$ will be stated shortly.

If we return to the sort of model considered above, allowing the σ^2's to depend on i and replacing, for example, τ^2_x by individual τ_i's, one for each i, we may write:

$$\text{ave } x_i = \gamma\tau_i,$$

$$\text{var } x_i = \sigma^2_{xi},$$

$$\text{ave } v_i = \tau_i + \varphi_i, \text{ and}$$

$$\text{var } v_i = \sigma^2_{vi},$$

where $(\tau_i, \gamma\tau_i)$ represents the related part of v_i and x_i, and φ_i is an additional part that we can appropriately assume to satisfy

$$\Sigma w_i (\tau_i - \tau_W)(\varphi_i - \varphi_W) = 0,$$

where

$$\tau_W = \frac{\Sigma w_i \tau_i}{\Sigma w_i} \text{ and}$$

$$\varphi_W = \frac{\Sigma w_i \varphi_i}{\Sigma w_i}$$

are the corresponding weighted means.

Algebra, postponed to the last section of this appendix, then shows that

$$\text{ave } \hat{\sigma}^2_{xi} = \sigma^2_{xi} = \text{var } x_i$$

is a sufficient condition for

$$\text{structural-b} = \frac{WSP + WSV}{WSS_x - WSV}$$

to be an appropriate estimate of the structural β relating y to x. This, then, is the weighted relative of

$$\text{structural-b} = \frac{\hat{c}ov(y,x) + \hat{\delta}^2_x}{\hat{v}ar(x) - \hat{\delta}^2_x}.$$

Notice that, in the weighted case, we have altered both numerator and denominator by the same factor, thus replacing means by weighted sums and slightly simplifying the arithmetic.

PROPER ADJUSTMENT FOR AGENT MEANS

Having found an estimate for the structural β, how should we use this estimate in adjusting agent death rates or agent SMR's to allow for differences in the corresponding SM's (standard death rates)? This question is not a trivial one. It can be answered easily in quite specific situations, but the answer in different specific situations is different.

Suppose, first, that

y_i = log SMR for unit i and

x_i = log SM for unit i,

and that the sort of detailed model used above in connection with the weighted analysis applies directly in the sense that the set of units (for this analysis, agents) is fixed.

We can again put

$$\text{ave } x_i = \gamma\tau_i \text{ and}$$

$$\text{ave } v_i = \tau_i + \varphi_i,$$

so that

$$\beta = \frac{1-\gamma}{\gamma}$$

is the reflection among the x's and y's here studied of the structural β among the x's and y's from which such an estimate is borrowed. It need not, however, now be true that the φ_i, which are the quantities we are trying to estimate by adjustment, are unrelated to the τ_i in any particular sense.

Now,

$$\text{ave } y_i = \text{ave } v_i - \text{ave } x_i = \tau_i + \varphi_i - \gamma\tau_i$$

$$= \frac{1-\gamma}{\gamma}\gamma\tau_i + \varphi_i ,$$

and

$$\text{ave}\left(y_i - \frac{1-\gamma}{\gamma} x_i\right) = \varphi_i ,$$

so that adjustment using structural-b, which estimates $(1-\gamma)/\gamma$, is appropriate.

If, instead, the i's had corresponded to a sample from a bivariate (Gaussian) population in which

$$\text{var } \tau_i = \tau^2,$$

$$\text{var } \varphi_i = \varphi^2, \text{ and}$$

$$\text{cov}(\tau_i, \varphi_i) = 0,$$

then

$$\text{ave } y_i = (1-\gamma)\tau_i + \varphi_i$$

and the average of φ_i among the i's yielding a given observed y_i would be

$$\frac{\varphi^2}{(1-\gamma)^2\tau^2 + \varphi^2} \cdot y_i .$$

As more detailed analysis would show, we would be led to use, not structural-b itself, but structural-b reduced by a factor estimating

$$\frac{\varphi^2}{(1-\gamma)^2\tau^2 + \varphi^2} .$$

In dealing with SMR's for agents, we are concerned with quite specific units, so that the first result "Use structural-b directly" applies.

ESTIMATING $\hat{\sigma}^2_{xi}$

We turn now to the calculation of estimates $\hat{\sigma}^2_{xi}$ of the individual σ^2_{xi}, which in our case is

σ^2_{xi} = sampling variance of log SM (sampl-var log SM).

Because

log SM = log(std deaths) - log EE,

it is clear that a large part of the assessment of sampl-var log SM is taken care of by the assessment of sampl-var log (std deaths), which was considered in Appendix 1.

The analysis there was conducted in two stages: first, the assessment of the sampling variance of $\hat{D}$ = std deaths on the assumption that all the observations followed Poisson distributions; and second, the assessment of the factor by which this result needed to be increased to make it applicable to the observed data. To make our calculations a little more transparent, we shall use "Poiss-var" for variances based on the Poisson assumption and "Poiss-cov" for analogous covariances, thus distinguishing these from "sampl-var" and "sampl-cov," which apply to actual sampling fluctuations (and from "var" and "cov," which would apply to all forms of difference among the quantities considered).

Simple algebra leads to this relation:

$$\text{Poiss-var log SM} = \text{Poiss-var log } \hat{D} - \frac{1}{\text{\# of randoms}},$$

where SM, $\hat{D}$, and the number of randoms all apply to the unit with which we are concerned (whatever its nature).

In Appendix 1 to Chapter IV-6 various estimates of

$$\text{expansion factor} = \frac{\text{sampl-var log } \hat{D}}{\text{Poiss-var log } \hat{D}}$$

are made, ranging from 1.40 to 1.05.

As a broad basis for analysis, we might well consider a range of factor from 1.0 to about 1.4. This is conveniently done by considering

$$\hat{\sigma}^2_{xi} = (1.0 \text{ to } 1.5)\left(\hat{\text{Poiss-var log }} \hat{D} - \frac{1}{\text{\# of randoms}}\right),$$

where $\hat{\text{Poiss-var log }} \hat{D}$ is a reasonable estimate of the Poisson-sampling variance of log $\hat{D}$. Here, the use of 1.5 corresponds to expansion factors ranging from 1.35, when the negative term is 30 percent of the preceding term, to 1.45, when it is 10 percent. (Most of our instances fall between 10 and 30 percent.)

THE POISS-VAR OF LOG SM

Using a notation somewhat analogous to that used in Appendix 1, we shall write, for any one unit that concerns us, provided that it is part of a single institution and thus shares a common blowup factor:

h = stratum identifier,

R_h = number of randoms observed in stratum h for the unit concerned,

k = "blowup factor" for the given unit,

p_h = the estimated death rate for stratum h, which we will treat as given (thus making the approximation found to be reasonably satisfactory in Appendix 1),

$\hat{E}$ = estimated number of exposed (or administrations) in the unit concerned, and

$\hat{D}$ = number of standard deaths for the unit.

The usual relations apply, namely:

$$\hat{E} = k\Sigma R_h,$$

$$\hat{D} = k\Sigma p_h R_h, \text{ and}$$

$$\text{Poiss-var } R_h \hat{=} R_h,$$

where $\hat{=}$ means "equal on the average."

Accordingly,

$$\text{Poiss-var } \hat{D} = k^2\Sigma p_h^2 \cdot \text{Poiss-var } R_h \hat{=} k^2\Sigma p_h^2 R_h,$$

$$\text{Poiss-var } \hat{E} = k^2\Sigma \cdot \text{Poiss-var } R_h \hat{=} k^2\Sigma R_h = k\hat{E}, \text{ and}$$

$$\text{Poiss-cov}(\hat{D},\hat{E}) = k^2\Sigma p_h \cdot \text{Poiss-var } R_h \hat{=} k^2\Sigma p_h R_h = k\hat{D},$$

so that we may use the right-hand values as natural estimates of the left-hand quantities. Using the usual relations for "propagation of error," we find:

$$\hat{\text{P}}\text{oiss-var log } \hat{D} \approx \frac{\hat{\text{P}}\text{oiss-var } \hat{D}}{(\hat{D})^2},$$

$$\hat{\text{P}}\text{oiss-var log } \hat{E} \approx \frac{\hat{\text{P}}\text{oiss-var } \hat{E}}{(\hat{E})^2} = \frac{kE}{\hat{E}} = \frac{k}{\hat{E}}, \text{ and}$$

$$\hat{\text{P}}\text{oiss-cov}(\log \hat{D}, \log \hat{E}) = \frac{\hat{\text{P}}\text{oiss-cov}(\hat{D},\hat{E})}{\hat{D}\hat{E}} = \frac{k\hat{D}}{\hat{D}\hat{E}} = \frac{k}{\hat{E}}.$$

Accordingly,

$$\hat{\text{P}}\text{oiss-var log SM} = \hat{\text{P}}\text{oiss-var}(\log \hat{D} - \log \hat{E}) = \hat{\text{P}}\text{oiss-var}(\log \hat{D}) - 2\frac{k}{\hat{E}} + \frac{k}{\hat{E}},$$

and, because

$$\frac{k}{\hat{E}} = \frac{k}{k\Sigma R_h} = \frac{1}{\#\text{ of randoms for whole unit}},$$

we obtain the desired result:

$$\hat{\text{P}}\text{oiss-var log SM} = \hat{\text{P}}\text{oiss-var}(\log \hat{D}) - \frac{1}{\#\text{ of randoms}}.$$

THE WEIGHTED ALGEBRA

Returning to the second section of this appendix, where we introduced

$$\text{WSS}_x = \sum_i w_i (x_i - x_w)^2 \text{ and}$$

$$\text{WSP} = \Sigma w_i (y_i - y_w)(x_i - x_w),$$

it is easy to show, by simple algebra, that these single-sum expressions for WSS_x and WSP are identically equal to suitable double-sum expressions, namely:

$$\text{WSS}_x = \frac{1}{2w_+}\sum_i\sum_j w_i w_j (x_i - x_j)^2 \text{ and}$$

$$\text{WSP} = \frac{1}{2w_+}\sum_i\sum_j w_i w_j (y_i - y_j)(x_i - x_j),$$

where

$$w_+ = \Sigma w_i .$$

These identities make it easy to see how the average values of various weighted expressions are related to the weights and to the assumed constituents of x and y, as also given above.

Building backward from later to earlier expressions, to keep the algebraic steps more clearly visible, we have, using the vanishing of covariances among the x's and v's, and the relation $y_i = x_i - v_i$:

$$\text{ave}(x_i - x_j)^2 = [\text{ave}(x_i - x_j)]^2 + \text{var}(x_i - x_j)$$

$$= (\gamma\tau_i - \gamma\tau_j)^2 + \sigma_{xi}^2 + \sigma_{xj}^2$$

$$= \gamma^2(\tau_i - \tau_j)^2 + \sigma_{xi}^2 + \sigma_{xj}^2 ;$$

$$\text{ave}[(v_i - v_j)(x_i - x_j)] = \text{ave}(v_i - v_j)\text{ave}(x_i - x_j)$$

$$= (\tau_i - \tau_j)\gamma(\tau_i - \tau_j) + (\varphi_i - \varphi_j)\gamma(\tau_i - \tau_j)$$

$$= \gamma(\tau_i - \tau_j)^2 + \gamma(\varphi_i - \varphi_j)(\tau_i - \tau_j)^2;$$

and

$$\text{ave}[(y_i - y_j)(x_i - x_j)] = \text{ave}[(v_i - v_j)(x_i - x_j)] - \text{ave}(x_i - x_j)^2$$

$$= \gamma(\tau_i - \tau_j)^2 - \gamma^2(\tau_i - \tau_j)^2 - \sigma_{xi}^2 - \sigma_{xj}^2$$

$$= (\gamma - \gamma^2)(\tau_i - \tau_j)^2 - (\sigma_{xi}^2 + \sigma_{xj}^2).$$

Moreover, relating the double-sum forms to the single-sum forms, we have:

$$\frac{1}{2w_+}\sum_i\sum_j w_i w_j (\tau_i - \tau_j)^2 \equiv \Sigma w_i (\tau_i - \tau_w)^2 ,$$

$$\frac{1}{2w_+}\sum_i\sum_j w_i w_j (\sigma_{xi}^2 + \sigma_{xj}^2) \equiv \frac{1}{2}\left[\frac{\Sigma w_j}{w_+}\ \Sigma w_i\sigma_{xi}^2 + \frac{\Sigma w_i}{w_+}\ \Sigma w_j\sigma_{xj}^2\right]$$

$$\equiv \Sigma w_i \sigma_{xi}^2 ,$$

and

$$\frac{1}{2w_+}\sum_i\sum_j w_i w_j (\varphi_i - \varphi_j)(\tau_i - \tau_j) \equiv \Sigma w_i(\varphi_i - \varphi_w)(\tau_i - \tau_j) = 0,$$

where we have used the defining constraint on the φ's. Accordingly, using the double-sum forms and the constancy of the w's,

$$\text{ave WSS}_x = \frac{1}{2w_+}\sum_i\sum_j w_i w_j \cdot \text{ave}(x_i - x_j)^2$$

$$= \gamma^2\frac{1}{2w_+}\sum_i\sum_j w_i w_j (\tau_i - \tau_j)^2 + \frac{1}{2w_+}\sum_i\sum_j w_i w_j (\sigma_{xi}^2 + \sigma_{xj}^2)$$

$$= \gamma^2\Sigma w_i(\tau_i - \tau_w)^2 + \Sigma w_i\sigma_{xi}^2;$$

and

$$\text{ave WSP} = \frac{1}{2w_+}\sum_i\sum_j w_i w_j \cdot \text{ave}[(y_i - y_j)(x_i - x_j)]$$

$$= (\gamma - \gamma^2)\Sigma w_i(\tau_i - \tau_w)^2 - \Sigma w_i\sigma_{xi}^2 .$$

Whence, setting

$$w_+\tau^2 = \Sigma w_i(\tau_i - \tau_w)^2$$

and

$$w_+\sigma_x^2 = \Sigma w_i\sigma_{xi}^2 ,$$

we have:

$$\text{ave WSS}_x = \gamma^2 w_+ \tau^2 + w_+ \sigma_x^2 ,$$

$$\text{ave WSP} = (\gamma - \gamma^2) w_+^{\ 2} - w_+ \sigma_x^2 ,$$

and

$$\frac{\text{ave WSP}}{\text{ave WSS}_x} = \frac{(\gamma - \gamma^2)\tau^2 - \sigma_x^2}{\gamma^2 \tau^2 + \sigma_x^2} .$$

Again we see that the structural β is $(\gamma - \gamma^2)/\gamma^2$ and that, if

$$\text{ave } \hat{\sigma}_x^2 = \sigma_x^2 ,$$

then

$$\text{ave } \left(\text{WSP} + w_+ \hat{\sigma}_x^2\right) = (\gamma - \gamma^2) w_+ \tau^2$$

and

$$\text{ave } \left(\text{WSS}_x - w_+ \hat{\sigma}_x^2\right) = \gamma^2 w_+ \tau^2 ,$$

so that,

$$\frac{\text{WSP} + w_+ \hat{\sigma}_x^2}{\text{WSS}_x - w_+ \hat{\sigma}_x^2}$$

is an appropriate estimate of the structural β as long as its denominator is not too small.

If $\hat{\sigma}_{xi}^2$ is an estimate of σ_{xi}^2, in the sense that

$$\text{ave } \hat{\sigma}_{xi}^2 = \sigma_{xi}^2 ,$$

and if we put

$$\text{WSV} = \Sigma w_i \hat{\sigma}_{xi}^2 ,$$

then

$$\text{ave WSV} = \text{ave } \Sigma w_i \hat{\sigma}_{xi}^2 = \Sigma w_i \sigma_{xi}^2 = w_+ \sigma_x^2 ,$$

so that we can put

$$\hat{\sigma}_x^2 = \frac{\text{WSV}}{w_+} .$$

and use

$$\frac{\text{WSP+WSV}}{\text{WSS}_x\text{-WSV}} = \text{structural-b}$$

as a natural estimate of structural β.

APPENDIX 6 TO CHAPTER IV-6

ASSESSMENT OF VARIOUS STRUCTURAL REGRESSION COEFFICIENTS

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This appendix discusses the calculation of various structural regression coefficients for the regression of log SMR on log SM, where SMR is a ratio of observed deaths to standard deaths and SM is the corresponding standard death rate. These coefficients are needed for the considerations of Appendix 4 to Chapter IV-6.

The calculations used here involve formulas developed and discussed in Appendix 5, particularly

$$\text{structural-b} = \frac{\hat{\text{cov}}(\log \text{SMR}, \log \text{SM}) + \hat{\sigma}_x^2}{\hat{\text{var}}(\log \text{SM}) - \hat{\sigma}_x^2}$$

(and its relatives) and

$$\hat{\sigma}_x^2 = (1.0 \text{ to } 1.5)\,(\hat{\text{Poiss-var}}(\log \text{std deaths})) - \frac{1}{(\#\text{ of randoms})}.$$

For the particular case where we are concerned with a weighted one-way analysis, the relative of the first of these formulas of greatest convenience is

$$\text{structural-b} = \frac{\text{WSP} + \text{WSV}}{\text{WSS}_x - \text{WSV}},$$

where

WSP = sum of (weights) × (log SMR - *) (log SM - **),

WSS_x = sum of (weights) × (log SM - **)^2,

WSV = sum of (weights) × ($\hat{\sigma}_x^2$ for individual unit),

* = weighted mean of log SMR, and

** = weighted mean of log SM.

Note that WSV still contains the adjustable factor of 1.0 to 1.5.

In giving details for various approaches, we shall follow a standard order for rows or columns, as set out in Table 1.

TABLE 1.--STANDARD ORDERING AND NUMBERING FOR ROWS OR COLUMNS OF TABLES LEADING TO ESTIMATES $\hat{\text{S}}$TRUCTURAL-b OF THE STRUCTURAL β

Row or column	Weighted sum of
(1)	Unity*
(2)	Product of deviations of log SMR and log SM from their means
(3)	Squared deviation of log SM from its mean
(4)	Estimated Poisson variance of log SM
(5)	Numerator "for 1.0" = (2) + (4)
(6)	Denominator "for 1.0" = (3) - (4)
(7)	$\hat{\text{S}}$tructural-b "for 1.0" = (5)/(6)
(8)	Numerator "for 1.5" = (2) + 1.5(4)
(9)	Denominator "for 1.5" = (3) - 1.5(4)
(10)	$\hat{\text{S}}$tructural-b "for 1.5" = (8)/(9)

*In equally weighted analyses (often called "unweighted"), an entry of n indicates the use of simple sums of squared deviations or cross-products.

"for 1.0" means $\hat{\sigma}_x^2 = \hat{\text{P}}$oiss-var log SM (see Appendix 5 to Chapter IV-6).

"for 1.5" means $\hat{\sigma}_x^2 = 1.5 \times \hat{\text{P}}$oiss-var log SM (see Appendix 5 to Chapter IV-6).

To assess how much of the naive superstandardization it is appropriate to apply to agent death rates, we face a nontrivial problem in selecting a source from which to borrow. Several approaches are discussed.

FIRST APPROACH

One place from which to borrow regression coefficients for use in adjusting agent comparisons for SM values is institution-to-institution differences. In Appendix 2 to Chapter IV-6, these differences have been studied for two basic standardizations: (1) the rather weak standardization based on age and shock-likelihood index, and (2) the stronger standardization based on 15 aggregation strata. Only the second is available

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TABLE 2.--CALCULATION OF STRUCTURAL b BASED ON (UNWEIGHTED) INSTITUTION-TO-INSTITUTION DIFFERENCES (AS TREATED IN APPENDIX 2 TO CHAPTER IV-6

	-(Sums of)-	
(1)	unity	34
(2)	cross-product of deviations	1.256
(3)	squares of deviations for log SM	8.631
(4)	Poiss-var (log SM)	0.308
	-(Values of)-	
(5)	numerator = (2) + (4)	1.564
(6)	denominator = (3) - (4)	8.323
(7)	structural-b for 1.0 = (5)/(6)	0.19
(8)	numerator = (2) + 1.5(4)	1.718
(9)	denominator = (3) - 1.5(4)	8.169
(10)	structural-b for 1.5 = (8)/(9)	0.21

Note: If structural β were zero, and 1.5 were an appropriate factor, the regression of y on x would be estimated by - (1.5)(0.308)/(8.169) = -0.06.

for the middle-death-rate operations separately; it provides the results set out in Table 2.

There is, however, reasonable ground for suspecting that the structural regressions between institutions and between agents may not be the same. Accordingly, we would not like to give too much weight to the results of borrowing a regression coefficient from institution-to-institution differences alone.

SECOND APPROACH

Let us select any one agent, say, halothane, and consider the 34 sets of results for the 34 institutions. We can try to assess a regression coefficient of log SMR on log SM here, and it may be appropriate to borrow such a regression coefficient to adjust agent SMR's, especially if such assessments within different agents lead to consistent regression coefficients. In doing this, it will be essential (1) to take account of the existence of σ_x^2 and try to estimate structural β's, and (2) to take account of differences in (estimated) variance of the various values of log SMR. We have learned (Appendix 5 to Chapter IV-6) how to cope with the first problem. Because we have only a one-way table, a weighted analysis can cope effectively with the second problem.

Table 3 sets out the results found for each of the five agents using

$$\text{wt} = \frac{170}{\text{estimated variance of log SMR}}.$$

The results vary somewhat from agent to agent, so that, because we will want to treat ether separately in the next approach, it seems reasonable to give a pooled result for all agents except ether, as well as for all agents including ether.

THIRD APPROACH

If we are willing to direct our attention to the comparison of only two agents at a time, we can take the view that we have 34 values of the log SMR difference,

$$\delta \log \text{SMR} = (\log \text{SMR for agent 1}) - (\log \text{SMR for agent 2}),$$

which are to be adjusted in view of the corresponding 34 values of the log SM difference,

$$\delta \log \text{SM} = (\log \text{SM for agent 1}) - (\log \text{SM for agent 2}).$$

We now need to use

$$\hat{\text{var}}\ \delta \log \text{SMR} = \sum_{i=1}^{2} \hat{\text{var}}(\log \text{SMR for agent i}) \text{ and}$$

$$\hat{\text{var}}\ \delta \log \text{SM} = \sum_{i=1}^{2} \hat{\text{var}}(\log \text{SM for agent i}),$$

thus leading to a new set of weights and a new adjustment for σ_x^2. The results for all 10 pairs of agents, separately and combined, are given in Table 4. We see that any combination including ether is persistently negative, whereas almost all other pairs give a positive regression, at least when 1.5 is used. Accordingly, it seems desirable to present separate results with and without ether, as well as for all pairs combined.

FOURTH APPROACH

We now turn to the question of a reasonable two-way analysis. The central unsolved problem is what to do with a rather irregular pattern of weights. The situation we must face is shown in Table 5, where the rough weights

$$\text{wt} = \text{nearest integer to } \frac{0.170}{\hat{\text{var}}\ \log \text{SMR}}$$

are shown, with zeroes replaced by hyphens for emphasis. Clearly, something must be done if we are to have a relatively straightforward analysis.

The simplest thing that we can do is to combine both rows and columns in a reasonable way. For the columns (agents), we would like to keep halothane separate, combine nitrous oxide-barbiturate with ether (as the apparently better two of the remaining four), and combine cyclopropane and Other (as the apparently worse two). This gives total weights of, approximately, 123, 122(= 91 + 31), and 143(= 64 + 79), which are

TABLE 3.--RESULTS FOR THE VARIOUS AGENTS ANALYZED SEPARATELY

		H	N-B	C	E	O	Combined (all)	Combined (omitting E)
				(Weighted sums)				
(1)	unity	130.5	91.7	95.7	34.7	82.9	435.5	400.8
(2)	$\hat{P}$oiss-var log SM	2.884	2.611	2.894	2.064	3.169	13.622	11.558
(3)	cross-product	1.554	3.212	-6.128	-3.864	5.127	-0.099	3.765
(4)	(log SM-mean)^2	34.951	27.236	46.015	16.608	28.000	152.81	136.20
				(Resulting values)				
(5)	numerator*	4.438	5.823	-3.234	-1.800	8.396	13.623	(15.423)
(6)	denominator*	32.067	24.625	43.116	14.544	24.831	139.183	(124.639)
(7)	structural-b (for 1.0)	0.14	0.19	-0.07	-0.12	0.33	0.10	(0.13)
(8)	numerator**	5.880	7.1285	-1.787	-0.768	9.880	20.334	(21.102)
(9)	denominator**	30.625	23.3195	41.674	13.512	23.247	132.377	(118.863)
(10)	structural-b (for 1.5)	0.19	0.31	-0.04	-0.06	0.42	0.15	(0.18)

*Of expression for estimated structural-b, using 1.0.
**Of expression for estimated structural-b, using 1.5.

TABLE 4.--RESULTS FOR ALL 10 AGENT PAIRS, SEPARATELY AND TOGETHER (COLUMN NUMBERS ASSIGNED ACCORDING TO TABLE 3, BUT INVOLVING δ LOG SMR AND δ LOG SM IN PLACE OF LOG SMR AND LOG SM, RESPECTIVELY; VALUES OF STRUCTURAL-b IN COLUMNS (7) AND (10) FOR FACTORS OF 1.0 AND 1.5, RESPECTIVELY)

Agent pair	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
H-N-B	134.44	-8.54	26.24	8.00	-0.54	18.24	-0.03	3.46	14.24	0.24
H-C	135.01	-8.64	40.33	8.34	-0.30	31.99	-0.01	3.87	27.82	0.14
H-E	61.10	-13.36	35.13	6.32	-7.04	28.81	-0.25	-3.88	25.65	-0.15
H-O	126.61	-7.46	29.77	9.07	1.61	20.70	0.05	6.15	16.16	0.38
N-B-C	104.05	-9.48	42.89	7.95	-1.53	34.94	-0.04	2.45	30.96	0.08
N-B-E	53.07	-19.90	28.48	6.23	-13.67	22.25	-0.61	-10.55	19.13	-0.55
N-B-O	100.09	-5.40	21.81	8.68	3.22	13.13	+0.24	+7.62	8.79	0.87
C-E	47.58	-17.78	36.63	6.10	-11.67	30.53	-0.38	-8.63	27.48	-0.31
C-O	113.12	-17.49	34.21	8.78	-8.71	25.43	-0.34	-4.32	11.09	-0.39
E-O	54.77	-12.41	27.95	6.70	-5.71	21.25	-0.26	-2.36	17.90	-0.13
Combined*										
No E	713.32	-57.01	195.25	50.82	-6.25	144.43	-0.04	19.16	119.02	0.16
E	216.52	-63.45	128.19	25.35	-38.09	102.84	-0.37	-25.42	90.16	-0.28
All	929.84	-120.46	323.44	76.17	-44.34	247.27	-0.18	-6.26	209.19	-0.03

*Weighted sums merely added together; corresponds roughly to weighting of mean squares, etc., in accordance with column (1).

No E = sums for all pairs not including ether; E = sums only for pairs including ether.

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TABLE 5.--ROUGH WEIGHTS, BASED ON EST VAR LOG SMR, ASSOCIATED WITH AGENT-INSTITUTION CELLS FOR MIDDLE-DEATH-RATE OPERATIONS (ONLY RELATIVE VALUES ARE IMPORTANT; - = 0)

Inst.	Agent				
	H	N-B	C	E	O
1	5	3	-	-	1
2	10	4	4	1	3
3	1	4	-	-	2
4	3	3	3	1	4
5	5	4	4	-	2
6	3	4	-	1	3
7	4	2	2	1	4
8	8	3	-	6	3
9	4	4	1	5	1
10	2	4	3	1	1
11	5	1	2	4	4
12	5	1	4	-	2
13	3	1	4	-	5
14	1	1	2	-	2
15	2	3	2	2	2
16	2	7	1	-	4
17	2	1	1	1	4
18	4	3	4	1	2
19	7	4	1	-	2
20	1	2	4	3	4
21	5	4	1	-	2
22	2	1	2	-	1
23	1	2	1	-	-
24	4	11	2	1	1
25	6	3	4	1	7
26	4	3	-	-	-
27	2	1	2	1	1
28	1	-	-	-	-
29	4	1	1	-	1
30	6	2	1	-	1
31	2	1	3	-	-
32	4	1	1	-	2
33	4	2	1	1	3
34	1	-	3	-	5

much more nearly balanced. For the rows (institutions), it seems natural to rearrange in order of values of SM (or log SM) for the institution as a whole before combining institutions and to avoid making too many combinations. These decisions lead to the results set out in Table 6, where we have shown in each cell the sum of the entries in the cells of Table 5 that have contributed to it. (This will be, roughly, the weight of this cell when properly calculated.)

The over-all efficiency, for unweighted analysis, of this aggregation can be estimated as:

$$\frac{(\#\text{ of cells})^2 / (\text{total wt})}{\text{sum of } (1/\text{wt})} = 78 \text{ percent.}$$

The 15 compound institutions involved seem to be enough to make the analysis otherwise satisfactory. Accordingly, we adopt the aggregation set out in Table 6 as the standard for this approach.

To deal with an analysis based on these aggregated cells, we have to sum the following quantities for the constituent cells of each aggregated cell:

EE = estimated administrations,

D = actual deaths,

$\hat{D}$ = standard deaths,

$\hat{\text{var}}\,\hat{D}$ = estimated variance of $\hat{D}$, and

R = number of randoms involved.

We can then calculate, for each aggregated cell, the various other quantities of interest, such as:

$$SMR = D/\hat{D},$$

$$SM = \hat{D}/EE,$$

$$\hat{\text{var}}\log D = \frac{1}{D},$$

$$\hat{\text{var}}\log \hat{D} = \frac{\hat{\text{var}}\,\hat{D}}{(\hat{D})^2},$$

$$\hat{\text{var}}\log SMR = \hat{\text{var}}\log D + \hat{\text{var}}\log \hat{D}, \text{ and}$$

$$\hat{\text{var}}\log SM \approx \hat{\text{var}}\log \hat{D} - (1/R).$$

Note that the use of $1/R$ as an adjustment term in the expression used for $\hat{\text{var}}\log SM$ is only an approximation, because we are combining across institutions, and hence across k's. Test calculations indicate, however, that the approximation is good enough.

TABLE 6.--CHOSEN COMBINATIONS OF ROWS AND COLUMNS, AND RESULTING ROUGH WEIGHTS

Institutions	H	N-B/E	C/O	(Range of $\log_e$ 100 SM)
17+28+30	9	4	7	(0.52 to 0.97)
3+27+31+34	6	7	16	(1.20 to 1.29)
1+6+14+26	13	12	8	(1.41 to 1.61)
8+13+23	12	12	13	(1.79 to 2.03)
20+21	6	9	11	(2.04 to 2.10)
12+19+22+32	18	7	15	(2.12 to 2.28)
15+16	4	12	9	(2.50 to 2.58)
4+9	7	13	9	(2.60 to 2.65)
5+10	7	9	10	(2.76 to 2.81)
11	5	5	6	(3.02)
7+29	8	4	8	(3.40 to 3.48)
24+33	8	15	7	(3.59 to 3.68)
18	4	4	6	(3.84)
25	6	4	11	(6.35)
2	10	5	7	(6.40)

Note: # of cells = 45, total wt = 388, sum of (1/wt) = 6.72.

Over-all efficiency = $\frac{(45)^2}{388(6.72)}$ = 78 percent.

We can now calculate various sums of squares and cross-products, and various sums for the unweighted two-way analysis of three compound agents by 15 compound institutions. The resulting values are shown, in mean form, in Table 7.

The same data, with the addition of values of $\hat{V}$ar log SMR, can be used to estimate the reduction in variance when "log SMR" is replaced by "log SMR adjusted for log SM." The resulting reductions are 25 and 30 percent for compound institutions and 5 and 25 percent for interactions, the two values in each pair corresponding to factors of 1.0 and 1.5, respectively. Accordingly, an estimated reduction of 25 percent seems to be ample.

TABLE 7.--RESULTS OF TWO-WAY ANALYSIS ON AGGREGATED CELLS

		Compound agents	Compound institutions	Interactions
(1)	Degrees of freedom	2	14	28
(2)	Mean cross-product ($\log_e$SMR with $\log_e$SM)	0.4411	0.1720	-0.0084
(3)	Mean square (of $\log_e$SM)	0.7182	0.7239	0.0690
(4)	Mean est Poiss samp var (for $\log_e$SM)	0.0186	0.0186	0.0186
(5)	Numerator (for 1.0)(= (2) + (4))	0.4597	0.1906	0.0102
(6)	Denominator (for 1.0)(= (3) - (4))	0.6996	0.7053	0.0504
(7)	Structural-b (for 1.0)(= (5)/(6))	0.66	0.27	0.20
(8)	Numerator (for 1.5)(= (2) + 1.5(4))	0.4690	0.1999	0.0195
(9)	Denominator (for 1.5)(= (3) - 1.5(4))	0.6903	0.6960	0.0417
(10)	Structural-b (for 1.5)(= (8)/(9))	0.68	0.29	0.47

Abstract of Chapter IV-7

Because shock is such an important variable in determining both a patient's prognosis and the choice of his anesthetic, an index of the estimated likelihood of shock was devised. This index was based on individual operations and on whether the operation was done as an emergency.

One hypothesis suggested for explaining the higher death rate associated with cyclopropane is that it is used more frequently when the patient is in danger from shock. The observation that cyclopropane has a higher death rate than halothane for all categories of shock likelihood casts doubt that this differential usage alone can explain the higher death rates.

CHAPTER IV-7. ANALYSIS OF MIDDLE-DEATH-RATE OPERATIONS USING A SHOCK-LIKELIHOOD INDEX

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The analysis presented here attempts to group individual operations into medically meaningful categories. This method differs from most of the other analyses of the middle-death-rate operations, in which the operations were grouped somewhat arbitrarily into 25 classes according to their observed death rates.

There are as many ways of grouping by medical criteria as there are criteria for rating operations. Thus, operations can be grouped according to the part of the body or according to the medical service under which the operation was performed. The criterion used here was the shock-likelihood index (SLI), the likelihood that a patient undergoing a given operation would suffer from shock. To sharpen the criterion, the likelihood of shock associated with each operation was assessed twice, once when the operation was elective (physical status 1, 2, 3, or 4) and once when it was an emergency procedure (physical status 5, 6, or 7).

This criterion was chosen, not only because of the importance of shock to the patient's prognosis, but also because of the suspicion that the high death rate observed after administration of cyclopropane in the Study was due in part to its selective use for patients in shock.

The operations were assigned to index categories;** the breakdown is shown in Table 1. The index runs from 1 to 5, with 1 signifying the smallest likelihood of shock and 5 signifying the greatest likelihood. It should be emphasized that these assignments were based not on the condition of the patient, but only on the operation and whether it was an emergency. If the operation or the physical status was unknown, SLI was coded as zero. These assignments were made for all the operations in the Study. It is much more effective, however, in the case of the seven low-death-rate and the four high-death-rate operations, to study the individual operations themselves. Given only a few operations having quite different death rates and also different usage patterns, what seems to be an agent comparison may really be an operation comparison. Consequently, this investigation is based only on the middle-death-rate operations.

Table 2 shows for each anesthetic agent the distribution of cases over the categories of SLI, as well as the observed death rates. It is clear that, although cyclopropane was used proportionally more often in SLI categories 4 and 5, this differential usage is not sufficient to account for the higher death rate associated with cyclopropane. Indeed, cyclopropane seems to suffer most in comparison with halothane and nitrous oxide-barbiturate in the lowest SLI categories. There is the possibility that even in the low-likelihood categories some patients will have suffered from shock. If these patients were also more likely to receive cyclopropane, this would explain, to some extent, the observed differences. It is one of the disadvantages of the nonrandomized study that, after all corrections have been made, there is no answer to such an argument, except to question whether the selection effects could have been so large. Two factors that tend to decrease the chance that the selection of poorer-risk patients might account for all the excess deaths after cyclopropane are: (1) cyclopropane was rarely used in several institutions, and (2) cyclopropane was used in

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TABLE 1.--OPERATIONS ASSIGNED TO THE FIVE SHOCK-LIKELIHOOD INDEX (SLI) CATEGORIES

If elective

SLI category 1	SLI category 2	SLI category 3	SLI category 4	SLI category 5
1 2 3 4	10 13 15 20	5 12 17 23	33 34 46 52	
6 7 8 9	21 22 26 28	27 32 36 43	57 59	
16 30 50 54	31 39 40 41	44 45 48 51		
55 60 71 87	42 47 58 62	56 67 68 70		
89 90 92 95	63 65 66 73	86 93		
	75 76 77 80			
	81 84 85 88			
	98 99			

If emergency

SLI category 1	SLI category 2	SLI category 3	SLI category 4	SLI category 5
2 3 4 7	9 30 31 54	5 6 20 21	1 10 12 13	33 34 36 45
8 50 71 87	80 81 84 85	26 55 60 73	15 16 17 22	48 51 57 59
89 90 92 95	88	76 77 98 99	23 27 28 32	67
			39 40 41 42	
			43 44 46 47	
			52 56 58 62	
			63 65 66 68	
			70 75 86 93	

some operations for which it is contraindicated. Such factors are very difficult to evaluate, however, and it is interesting to note that standardizing on the six SLI categories has done as much as any other single variable to eliminate the differences between agents.

To explore further the effects of controlling for SLI, we performed a version of the analysis described in Chapter IV-4, using the variables SLI and age. Age was grouped into five categories so that the cross-classification of SLI and age defined 30 categories on which to standardize the common practices. These were then jackknifed to produce over-all death rates comparable with those in Table 2 of Chapter IV-4. These death rates are shown in Table 3.

The variables in analysis VIII are operation (coded into 25 categories), physical status, and age. Analysis VIII gives a smaller range of differences between death rates than does the SLI × age analysis. The significance of the agent differences for analysis VIII is discussed in Chapter IV-4.

To conclude, the SLI analyses suggest that the selective use of cyclopropane for patients in shock is a contributing factor to the high cyclopropane death rate. They also indicate, however, that that factor could hardly account for all the observed differences in death rates.

TABLE 2.—AGENT VS. SLI MIDDLE-DEATH-RATE OPERATIONS

Distribution, %

SLI category	Agent					
	H	N-B	C	E	O	All
Unknown	16.3	16.5	15.0	16.6	17.9	16.4
1	25.0	28.8	24.8	23.9	23.6	25.5
2	39.5	34.7	33.7	34.3	35.7	36.3
3	14.0	14.9	12.8	18.9	14.4	14.6
4	4.7	4.6	10.8	5.5	7.1	6.1
5	0.7	0.5	2.8	0.8	1.3	1.1
Total EE (in thousands)	145.7	100.8	68.1	44.2	67.2	426.0
	Death rates					
Unknown	0.01781	0.01512	0.02937	0.01920	0.02342	0.01999
1	0.00405	0.00419	0.00582	0.00386	0.00801	0.00492
2	0.01018	0.01158	0.02192	0.01237	0.01793	0.01368
3	0.02968	0.02856	0.03786	0.02233	0.03797	0.03089
4	0.07758	0.07976	0.08818	0.07466	0.10723	0.08625
5	0.16867	0.19932	0.17865	0.17483	0.23408	0.18941
Over-all	0.01727	0.01709	0.03401	0.01854	0.02988	0.02207
Standardized death rate	0.01922	0.01969	0.02781	0.01900	0.02793	0.02207
Standard (ratio)	0.87096	0.89232	1.26010	0.86073	1.26539	
Indirect MR	0.85973	0.87653	1.17859	0.84430	1.28205	

TABLE 3.--OVER-ALL DEATH RATES ESTIMATED FROM SLI × AGE AND FROM ANALYSIS VIII OF CHAPTER IV-4 FOR THE MIDDLE-DEATH-RATE OPERATIONS

	Agent				
	H	N-B	C	E	O
SLI × age	0.0205	0.0129	0.0281	0.0136	0.0258
Analysis VIII	0.0192	0.0199	0.0254	0.0181	0.0241

CHAPTER IV-8. AFTERWORD FOR THE STUDY OF DEATH RATES

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COMPARISON OF ANESTHETICS

This section summarizes the results of the study of death rates. It begins with the raw results of Chapter IV-2, continues with the standardization of death rates on one variable, and then turns to the analyses for several variables of Chapters IV-3 through IV-7, including some measures of reliability of differences. It closes with a discussion of the limitations of the study of death rates.

In speaking of death rates following the administration of an anesthetic and surgery, brevity of language is likely to suggest erroneously that a given death rate is wholly attributable to the anesthetic agent used, whereas the study asks whether any of it is. The cause-and-effect question could well be held in abeyance until the summary is completed. To eliminate the convenience of referring to a death rate by its associated anesthetic would make the following description longer and cloudier.

The Unadjusted Death Rates (Chapter IV-2)

In all the analyses of death rates, the many administrations of anesthetics were grouped into categories labeled "halothane," "nitrous oxide-barbiturate," "cyclopropane," "ether," and "Other." Frequently, also, the analyses were applied separately to three groups of operations: the seven low-death-rate operations, the many middle-death-rate operations, and the four high-death-rate operations. Table 1 displays the compositions and sizes of the groups. Only about 5 percent of the deaths followed the low-death-rate operations, although they accounted for about 43 percent of the cases. The middle-death-rate group accounted for about 57 percent of the deaths and about 50 percent of the cases. The high-death-rate group accounted for the remaining 38 percent of the deaths and 7 percent of the cases. The raw death rates corresponding to the anesthetic agents showed considerable differences, as displayed in Table 2. Naturally, such rates cannot be accepted at face value because of sources of bias, such as the preferential use of some anesthetics for some hazardous operations or for patients in poor physical status. Nevertheless, the findings of the whole study are similar to the findings of this unadjusted table, except that the differences given here exaggerate the results found after adjustment. Generally speaking, cyclopropane and Other had higher death rates than halothane, nitrous oxide-barbiturate, or ether, and the latter three had similar death rates over-all.

Adjustments for One Variable (Chapter IV-2)

To make allowances for some of the sources of bias, individually, Chapter IV-2 showed the effects of adjustments allowing for the different frequencies of use of the several anesthetic agents. We summarize in Table 3 the effects of these one-variable adjustments for physical status, age, institution, and operation. Ratios greater than 1 imply higher death rates than average. This table gives the same general impression as the unadjusted table (Table 2).

In every comparison, Other has an indirectly standardized mortality ratio higher than average.

In the low-death-rate operations, ether and nitrous oxide-barbiturate have ratios lower than average, and halothane and cyclopropane ratios a bit higher than average.

In the middle-death-rate operations, halothane, nitrous oxide-barbiturate, and ether have similar lower ratios, and cyclopropane and Other have higher ratios.

In the high-death-rate operations, ether has the lowest ratios, halothane the next-lowest ratios, and nitrous oxide-barbiturate and cyclopropane slightly higher ratios. Both ether and cyclopropane vary a great deal from one adjustment to another, which makes us want to look at rates adjusted for several variables simultaneously.

No adjustment method is entirely satisfactory. In Table 3, every starred number is an indirectly standardized ratio (for definitions, see

TABLE 1.--SUMMARY OF HIGH-, MIDDLE-, AND LOW-DEATH-RATE GROUPS OF OPERATIONS

Operation group	Operation codes included	Estimated exposed		Deaths		Death rate, %*
		Number (in thousands)	%	Number	%	
High-death-rate	12,33,44,48**	61.7	7.2	6,354	37.8	9.34
Low-death-rate	1,3,55,60,65, 73,90***	366.3	42.9	844	5.0	0.23
Middle-death-rate	All others****	426.0	49.9	9,615	57.2	2.21
All	--	854.0	100.0	16,813	100.0	

*Death rate computed as D/(D+EE).
**12: craniotomy,
33: heart and great vessel with pump,
44: exploratory laparotomy, and
48: large bowel.
***Mouth and dental; eye, all; dilatation and curettage, etc.; hysterectomy; herniorrhaphy; cystoscopy; and plastic surgery.
****Except mammoplasty, which was omitted.

Source: Table 1 of Chapter IV-2; Appendix 1 to Chapter IV-5.

TABLE 2.--UNADJUSTED DEATH RATES IN PERCENT AND STANDARD MORTALITY RATIOS FOR EACH ANESTHETIC AGENT AND LOW-, MIDDLE-, AND HIGH-DEATH-RATE GROUPS OF OPERATIONS

Group of operations	Unadjusted death rates, %					
	Anesthetic agent					
	H	N-B	C	E	O	All
Low-death-rate	0.27	0.20	0.26	0.13	0.29	0.23
Middle-death-rate	1.76	1.74	3.52	1.89	3.08	2.26
High-death-rate	9.5	11.4	10.9	6.5	13.3	10.3
All	1.91	1.51	2.61	1.37	2.57	1.97

Source: Table 1 of Chapter IV-2.

Group of operations	Standard Mortality Ratios				
	Anesthetic agent				
	H	N-B	C	E	O
Low-death-rate	1.2	0.9	1.1	0.6	1.3
Middle-death-rate	0.8	0.8	1.6	0.8	1.4
High-death-rate	0.9	1.1	1.1	0.6	1.3
All	0.97	0.77	1.33	0.70	1.30

the second section of Chapter IV-2) that is considerably lower than the directly standardized ratio. The disagreement probably means that the number should be viewed with a little more suspicion than usual. The indirect ratios are less sensitive to large death rates based on few cases, but may mislead by seeming to be applicable when they are not, as in the ether ratio for high-death-rate operations; ether was rarely used in the heart operation (code 33).

TABLE 3.--INDIRECT MORTALITY RATIO BY ANESTHETIC AGENT BASED ON "ALL ANESTHETICS" POPULATION

Standardized for:	Agent				
	H	N-B	C	E	O
	Low-death-rate operations				
Physical status	1.08	0.84	0.97	0.73*	1.47
Age	1.11	0.72	1.28	0.71	1.42
Institution	1.10	0.91	0.98**	0.64	1.32*
Operation	1.01	0.88	1.21	0.58	1.32
	Middle-death-rate operations				
Physical status	0.87	0.87	1.22	0.92	1.15
Age	0.82	0.77	1.54	0.83	1.27
Institution	0.80	0.76	1.32**	1.05*	1.40
Operation	0.83	0.91	1.32	0.74	1.26
	High-death-rate operations				
Physical status	0.99	1.07	0.97	0.78	1.11
Age	0.95	1.14	1.03	0.61	1.23
Institution	0.96	0.99*	1.01**	0.72**	1.32
Operation	0.85	1.04	1.24	0.74**	1.25

*The directly standardized ratio is more than 20 percent higher.
**The directly standardized ratio is more than 50 percent higher.

Source: Tables 2, 3, and 4 of Chapter IV-2.

Adjustments for Several Variables

Smoothed Contingency-Table Analysis (Chapter IV-3).

The smoothed contingency-table analysis uses data from several variables to make estimates of death rates in cells adjusted simultaneously for such variables as age, physical status, and sometimes operation and sex.

Selected lines from the many large tables in Chapter IV-3 illustrate in Table 4 the detail of the estimates for cells where more data are available. In the low-death-rate operations, adjusted for age, physical status, and sex, the results presented are rather similar for the several anesthetic agents. The largest difference in the upper panel, 0.08, would represent four deaths in 5000 operations.

In the middle-death-rate operations, adjusted for operation category (operations were grouped into five categories according to death rate), physical status, and age, ether usually appears to have had the lowest rate, nitrous oxide-barbiturate and halothane to have had higher and similar rates, and cyclopropane and Other usually to have had the highest rates.

In the high-death-rate operations, adjusted for operation code, risk, and age, halothane, ether, and nitrous oxide-barbiturate had similar rates (after operations 48 and 44, for which the comparison is readily made). Halothane's high rate for craniotomy in the 50-69 age group disagrees with its lower rate for the 10-49 age group. For heart and great vessel operations with pump, halothane had a lower rate than nitrous oxide-barbiturate. Cyclopropane and Other had somewhat higher rates for operations 48 and 44, and they were little used in operations 12 and 33.

By considering rankings of the anesthetics on observed death rates for subclasses of procedures controlled on several variables, we can get one summary of these results, including evidence from rows of the tables not presented in this section. Table 5 shows the results of such rankings.

It must be recalled that we have set Other aside because it so systematically has a high death rate and because of the heterogeneity of its anesthetics. The implications of the rankings are as follows:

(1) For the low-death-rate operations, cyclopropane usually had the highest death rates among the four anesthetic agents, and nitrous oxide-barbiturate and ether the lowest, with halothane having about the average rank. The differences between the rankings are significant beyond the 0.5 percent level.

(2) For the middle-death-rate operations, cyclopropane systematically had higher ranks, and halothane, nitrous oxide-barbiturate, and ether had similar sets of ranks. The differences between the agents are significant far beyond any of the usual levels (see the cautionary remark below, however).

(3) In the high-death-rate operations, cyclopropane also ranked high, except for operation 33, where the ranking data are sparse and the number of cyclopropane cases low, and operation 12, for which it was rarely used. Halothane had the lowest summed ranks for operations 48 and 44, was below average for operation 33, and was one point above average for operation 12. A fair summary would say that for the high-death-rate operations halothane had the best record, based on ranks. Nitrous oxide-barbiturate was a close second, and ether, as usual, was variable. Taking the operations one at a time, the anesthetic differences are not significant at any of the usual levels.

The significance tests reported on the ranks may be subject to some correlation owing to the appearance of the same institutional components in different rankings. The effect of adjusting for institutional correlation, if it could

TABLE 4.--ILLUSTRATIVE DEATH RATES IN PERCENT FROM THE SMOOTHED CONTINGENCY-TABLE ANALYSIS

LOW-DEATH-RATE OPERATIONS
Female; known physical status; at least 5000 estimated exposed

Physical status	Age	Agent				
		H	N-B	C	E	O
1,2	0-9	0.12			0.06	0.04
1,2	10-49	0.06	0.04	0.04	0.06	0.06
1,2	50-69	0.20	0.20	0.18		

Source: Tables 7, 9, 11, and 13 of Chapter IV-3.

All ages; both sexes; at least 2000 estimated exposed

Physical status	Agent		
	H	N-B	C
3,4	2.2	1.9	2.4
5	0.11	0.12	0.13

Source: Tables 8 and 10 of Chapter IV-3.

MIDDLE-DEATH-RATE OPERATIONS
Risk 1, 2, 5; at least 1000 estimated exposed

Operation category	Age	Agent				
		H	N-B	C	E	O
1	10-49	0.08	0.08	0.14	0.07	0.13
1	50-69	0.40	0.33	0.46	0.27	0.54
2	10-49	0.43	0.62	0.47	0.22	0.85
2	50-69	1.2	1.3	1.7	1.3	1.8
3	10-49	0.61	0.56	0.93	0.24	0.86
3	50-69	1.9	2.1	2.6	2.4	2.6
4	10-49	1.0	1.1	1.3	0.36	1.7
4	50-69	3.0	3.0	3.7	2.2	3.7
5	10-49	2.7		2.6		
5	50-69	4.1		6.1		

Source: Table 16 of Chapter IV-3 (also mainly available in Table 19 of Chapter IV-3).

HIGH-DEATH-RATE OPERATIONS
Risk 1, 2, 5; at least 500 estimated exposed

Operation	Age	Agent				
		H	N-B	C	E	O
48 (large bowel)	10-49	1.3	1.2	1.5	0.9	0.8
	50-69	2.2	2.1	3.1	2.0	3.6
44 (exploratory laparotomy)	10-49	1.3	1.8	2.4	1.8	2.1
	50-69	3.5	3.3	6.4	3.2	5.4
12 (craniotomy)	10-49	3.9	5.6		3.4	
	50-69	9.5	6.3		4.4	
33 (heart and great vessel with pump)	10-49	7.7	12.2			
	Risk 3,4,6					
	10-49	12.7	20.8			

Source: Table 27 of Chapter IV-3.

be done, would probably be to reduce the significance of a set of differences. The significance of the middle-death-rate results would probably still stand, but that of the low-death-rate differences might be weakened from 0.5 to 5 percent. We defer the over-all death-rate summaries in percent and the special study of cholecystectomies based on the smoothed contingency-table analysis to a later discussion.

The Smear-and-Sweep Analysis of the Middle-Death-Rate Operations (Chapter IV-4).

A second way to adjust death rates for many background variables simultaneously is offered by the smear-and-sweep analysis. In this analysis, a test of the significance of the differences between anesthetic death rates is based on the consistency of the differences in rates from one institution to another. By exploring many possible related analyses, it was shown that the results (except for ether) were not very sensitive to various choices in the method. We concentrate here on the preferred analysis VIII, which adjusted for age, physical status, and operation category. Table 6 gives means and standard errors for analysis VIII. Ether's large standard error reflects its limited use in some institutions.

Because the extreme variation in ether death rates disturbed the analysis of variance of the institutional effects, a reanalysis was required with ether omitted. Table 7 shows the differences at the 5 percent level of significance.

A ranked analysis of variance, like that carried out for the data in Chapter IV-3, ranks the death rates (actually pseudo-rates) associated with the five anesthetic agents within each hospital. Then these ranks are summed. Low ranks were given to low death rates. The sums of the ranks were:

H	N-B	C	E	O
81	83	121	109	116

The differences were significant beyond the 0.5 percent level.

A further, especially sensitive analysis (Table 8 of Chapter IV-4) found significant differences at the 5 percent level in the death rates for the pairs of anesthetics halothane-cyclopropane, halothane-Other, and nitrous oxide-barbiturate--cyclopropane, where cyclopropane and Other had the higher rates.

Analysis by Regression (Chapter IV-5).

Five different analyses provide summary statistics for the death rates.

(1) Smoothed contingency tables: Using the analyses of Chapter IV-3, new strata were formed within each operation group (low-, middle-, and high-death-rate). For the middle-death-rate group, the strata in one study (model A) were operation category, physical status, age, and sex, and in another (model B), operation category, physical status, and age. We present here the model B results.

(2) ORLA regression: Using the variables operation, risk (physical status), length of operation, and age (the four variables are abbreviated "ORLA"), a cubic polynomial was fitted, strata were created, and summaries were computed.

TABLE 5.--SUMMARY OF SUMMED RANKS OF OBSERVED DEATH RATES

Low totals imply low death rates

LOW-DEATH-RATE OPERATIONS

Physical status	Agent				
	H	N-B	C	E	Total
Unknown	25	13.5	26.5	15	80
1,2	22	18	23	17	80
3,4	20	19	24.5	16.5	80
5	21	19.5	21.5	18	80
6	19	21	26.5	13.5	80
Total ranks	107	91	122	80	400

Source: Table 15 of Chapter IV-3.

MIDDLE-DEATH-RATE OPERATIONS

Operation category	Agent				
	H	N-B	C	E	Total
1	27	23	42	28	120
2	27	28	40	25	120
3	19	17	30	24	90
4	23	32	42	23	120
5	23	26	34	17	100
Total ranks	119	126	188	117	550

Source: Table 20 of Chapter IV-3.

HIGH-DEATH-RATE OPERATIONS

Operation	Agent				
	H	N-B	C	E	Total
48 (large bowel)	11	13	18	18	60
44 (exploratory laparotomy)	17	19	27	17	80
12 (craniotomy)	11	13	*	6	30
33 (heart and great vessel with pump)	5	9	4**	*	18

*Too few cases to rank.
**Based on small numbers of cases.

Source: Table 28 of Chapter IV-3.

(3) Overlapping definition: The ORLA regression was redone to see whether the category Other had been treated unfairly by including in it mixtures of anesthetics containing halothane, nitrous oxide-barbiturate, cyclopropane, and ether. To adjust for this, every administration of an anesthetic was counted in every major category in which it appeared and excluded from Other, which then contained no procedures using halothane, nitrous oxide-barbiturate, cyclopropane, or ether. For example, if a mixture of halothane and cyclopropane were administered, the case would be counted in the halothane and cyclopropane categories and omitted from Other.

TABLE 6.--MEANS AND STANDARD ERRORS OF THE DEATH RATES IN PERCENT BASED ON SMEAR-AND-SWEEP FOR MIDDLE-DEATH-RATE OPERATIONS

	Agent				
	H	N-B	C	E	O
Death rate	1.92	1.99	2.54	1.81	2.41
Standard error	0.27	0.18	0.17	0.48	0.20

Source: Analysis VIII of Tables 2 and 3 of Chapter IV-4.

TABLE 7.--TWO-WAY ANALYSIS OF VARIANCE OF HOSPITAL AND ANESTHETIC DIFFERENCES IN DEATH RATE (ETHER OMITTED) FOR MIDDLE-DEATH-RATE OPERATIONS

	Degrees of freedom	Mean square	F	5% critical value
Hospitals	33	0.000273	2.56	1.57
Agents	3	0.000314	2.94	2.70
Error	99	0.000107		

Source: Table 5 of Chapter IV-4.

(4) Age-SLI regression: The shock-likelihood index (SLI) of Chapter IV-7 was combined with age, and again a cubic polynomial was fitted to give strata. All operations were considered simultaneously.

(5) Cholecystectomies: A special study of cholecystectomies based on the analysis in Chapter IV-3 is presented because of its interest in the question of hepatic necrosis.

In Table 8, the results of these five studies are assembled for easy comparison. They show, as usual, that nitrous oxide-barbiturate and ether had the low death rates in the low-death-rate operations, that cyclopropane and Other had the high death rates in the middle- and high-death-rate operations, and that the rates for halothane and nitrous oxide-barbiturate are closely matched in the middle- and high-death-rate operations. As explained elsewhere, rates for ether are somewhat unreliably determined.

Over all operations, the smoothed contingency-table analysis and the ORLA regression agree that halothane, nitrous oxide-barbiturate, and ether had much the same low rates, and that cyclopropane and Other had higher rates. The age-SLI regression gives

TABLE 8.--DEATH RATES IN PERCENT FROM THE THREE REGRESSION STUDIES OF CHAPTER IV-5

	Agent				
	H	N-B	C	E	O
LOW-DEATH-RATE OPERATIONS					
Smoothed analysis	0.25	0.16	0.25	0.18	0.33
ORLA* regression	0.23	0.19	0.27	0.17	0.32
Overlapping definition	0.25	0.21	0.28	0.23	0.40
MIDDLE-DEATH-RATE OPERATIONS					
Smoothed analysis	1.95	1.95	2.79	1.79	2.55
ORLA regression	2.04	1.94	2.75	1.73	2.56
Overlapping definition	2.09	1.79	2.61	1.93	3.35
Cholecystectomies	2.03	2.62	2.51	2.30	2.84
HIGH-DEATH-RATE OPERATIONS					
Smoothed analysis	8.4	9.1	11.0	8.1	10.8
ORLA regression	8.4	9.0	11.7	9.9	10.8
Overlapping definition	8.2	8.2	10.4	9.4	17.1
TOTAL OPERATIONS					
Smoothed analysis**	1.68	1.69	2.28	1.55	2.17
ORLA regression**	1.71	1.68	2.32	1.62	2.17
Overlapping definition	1.73	1.56	2.15	1.63	3.06
Age-SLI regression	1.93	1.72	2.16	1.52	2.33
Unadjusted rates	1.91	1.51	2.61	1.37	2.57

*ORLA means control for operation, risk (physical status), length of operation, and age.
**Using weights of 43 percent for low-, 50 percent for middle-, and 7 percent for high-death-rate operations, as shown in Table 1.

Source: Table 1 of Chapter IV-2; Tables 1, 5, and 6 of Chapter IV-5.

somewhat different results, and that needs comment. This index does not take account of physical status, except for the distinction between emergency and nonemergency operations, and it analyzes low-, middle-, and high-death-rate operations simultaneously. The smoothed and ORLA analyses not only stratify on death rate in operations, but break down the high-death-rate operations to single codes, a matter of some importance in that these four operations accounted for nearly 40 percent of the deaths. Consequently, we regard the age-SLI index as inferior for this purpose.

The attempt to be more fair to Other by omitting cases in which a patient received two or more major anesthetic agents (a possible indication of a patient in trouble) from that category left Other with noticeably higher rates, up 1 percent over-all, and reduced the rates for cyclopropane and nitrous oxide-barbiturate by about one-seventh of 1 percent.

Far from showing high death rates in the cholecystectomies, halothane had the lowest rate of any of the anesthetics. However, the evidence from the rankings for significance of differences is weak, so we must leave the matter as an indication favoring halothane, rather than a firm finding that halothane actually had a lower rate than any of the others.

To search further into the sampling stability of the halothane-cyclopropane difference, their death rates adjusted for ORLA were compared in some hospitals for the middle-death-rate operations. These hospitals were chosen because each used both anesthetics in at least 20 percent of its operations. In 10 of 11 hospitals, halothane had the lower rate, a result significant at about the 1 percent level. A similar analysis on the high-death-rate operations favored halothane in eight of 11 hospitals, which is indicative but not significant.

Analysis by Aggregation (Chapter IV-6).

In Chapter IV-6, multiple adjustments for interfering variables are made in a manner somewhat different from that in Chapter IV-5. In the cross-classification created by these variables, death rates can be calculated for each cell, and then aggregated in death-rate order. Death rates can then be calculated and standardized against the strata. Although the data were treated quite differently, the death-rate results are so similar to those of Table 8 that it would not be helpful to reproduce them. Nevertheless, the close agreement shows the stability of the results when substantially different techniques adjust for similar variables.

Because cyclopropane was used more often than halothane in emergency operations, the mortality rates in the middle-death-rate operations were checked. The comparison was adjusted for ORLA, and, although all death rates are reduced when emergencies are removed, cyclopropane's mortality ratio rises about 6 percent, as shown in Table 9, whereas those for halothane, Other, and nitrous oxide-barbiturate rise 2, 2, and 4 percent, respectively. Only ether lowers its ratio when the emergencies are removed.

Consistency among Institutions of Differences between Anesthetic Agents (Chapter IV-6)

We study the stability of anesthetic differences among the 34 institutions for two reasons: (1) it enables institutional effects to be disentangled from the anesthetic comparisons

TABLE 9.--VARIOUS MORTALITY RATIOS OBTAINED BY AGGREGATION FROM MIDDLE-DEATH-RATE OPERATIONS

Emergency	Agent				
	H	N-B	C	E	O
ORA --	0.90	0.91	1.21	0.80	1.14
ORLA In	0.91	0.92	1.16	0.85	1.11
ORLA Out	0.93	0.96	1.23	0.82	1.13

Source: Tables 5 and 12 of Chapter IV-6.

(their entanglement was discussed above, under "Adjustments for One Variable"); and (2) it is more reliable to study the differences from institution to institution that recur consistently. Three approaches to studying transinstitutional stability were undertaken.

First, the agent comparisons were studied separately in each institution (for the middle-death-rate operations) after aggregation stratification for age, risk (physical status), and operation. The indirectly standardized mortality ratio (ISMR) obtained in this analysis for each anesthetic agent over all institutions appears in the first line of Table 9. Two rank methods, taking account of the variability and the magnitude of the anesthetic differences, were applied, and a more delicate technique, taking account of both factors at once, was developed and applied. The results were four highly significant differences: halothane and nitrous oxide-barbiturate had lower rates than cyclopropane and Other. A less clear, although statistically significant, finding of ether having higher rates than nitrous oxide-barbiturate also emerged, but we put little confidence in this conclusion because ether comparisons typically differ under various methods of analysis.

Second, we identified, for each pair of anesthetics, institutions that used both of the pair "frequently" (in 10 or 15 percent of all operations). When an anesthetic in a pair had the lower ORA-adjusted ISMR for the middle-death-rate operations in an institution, it scored a point in its favor. Winning a large preponderance of institutional comparisons indicated interinstitutional stability of the comparison. Halothane compared favorably with cyclopropane, with high significance. Less strong indications were found for halothane having lower rates than Other and nitrous oxide-barbiturate having lower rates than cyclopropane. This analysis did not demonstrate the favorable comparison of nitrous oxide-barbiturate with Other, found in the first analysis.

Third, we undertook a simple, easily understood study based on operations performed often in nearly every institution, standardizing only for the frequency with which each operation was performed in each institution. For this purpose, six, mostly middle-death-rate, operations were chosen that accounted for about 16 percent of the total estimated exposed. The analysis produced the usual halothane-cyclopropane, nitrous oxide-barbiturate--Other, and halothane-Other differences at the 5 percent level of significance, plus a strong suggestion that nitrous oxide-barbiturate had a lower rate than cyclopropane. Lack of adjustment for other important variables would be a reasonable criticism of the study; nevertheless, many will find it reassuring that a simple analysis supports the more complicated ones.

Finally, the four high-death-rate operations, analyzed individually, by the first two methods exhibited no significant comparisons stable across institutions.

The Shock-Likelihood Index (Chapter IV-7)

Because cyclopropane is said to be used often for operations on patients in shock and for operations likely to produce shock, a special study investigated the possible bias of such selective use. Each operation code was subjectively rated, separately as an emergency and as a nonemergency, into five categories on the basis of the likelihood of association with shock. It must be emphasized that the rating was not based on the condition of individual patients in this Study.

A study of the middle-death-rate operations found that, although cyclopropane was used proportionately more often in the higher SLI categories, 4 and 5, the major contribution to its higher standardized death rates came from the differentials in SLI categories 1, 2, and 3, which include 77 percent of its cases (Table 10). In a further study of the middle-death-rate operations, age and SLI were combined to examine the death rates. The results for age-SLI and for Chapter IV-4 are compared in Table 11; however, it must be remembered that the age-SLI analysis has little control for physical status and that the emergency-nonemergency distinction, although it affected the death rates considerably, did not reduce cyclopropane's mortality ratio in Chapter IV-5. For the purpose of comparing over-all death rates, we do not believe that age-SLI is as effective as the smoothed contingency-table analysis or the ORLA regression or, in the middle-death-rate operations, analysis VIII of smear-and-sweep and the analyses of Chapter IV-6.

To what extent have the original death rates been changed by the adjustments? Table 12 shows that Other, cyclopropane, and halothane reduced their rates by 0.4, 0.3, and 0.2 percent respectively, and nitrous oxide-barbiturate and ether increased their rates by 0.2 and 0.3 percent, respectively, from the original unadjusted figures. The relative positions of halothane and cyclopropane are scarcely changed.

Anesthetic Death Rate

In this summary, we have alluded to differences in death rates of the order of half of 1 percent or more. Although the death rates themselves cannot be attributed to the anesthetic agent, the differences in the adjusted or standardized death rates do imply rates for which the differences between the anesthetics and their procedures might be held partly accountable. Beecher and Todd (1) found the anesthetic death

TABLE 10.--DEATH RATES IN PERCENT FOR SHOCK-LIKELIHOOD CATEGORIES AND ANESTHETICS FOR MIDDLE-DEATH-RATE OPERATIONS

SLI	Agent					% of all operations in category
	H	N-B	C	E	O	
Unknown	1.78	1.51	2.94	1.92	2.34	16
1	0.40	0.42	0.58	0.39	0.80	26
2	1.02	1.16	2.19	1.24	1.79	36
3	2.97	2.86	3.79	2.23	3.80	15
4	7.8	8.0	8.8	7.5	10.7	6
5	16.9	19.9	17.9	17.5	23.4	1
Standardized death rate	1.92	1.97	2.78	1.90	2.79	100

Source: Table 2 of Chapter IV-7.

TABLE 11.--COMPARISONS OF SEVERAL STANDARDIZATIONS OF DEATH RATES IN PERCENT FOR MIDDLE-DEATH-RATE OPERATIONS

	Agent				
	H	N-B	C	E	O
Age-SLI	2.05	1.29	2.81	1.36	2.58
Analysis VIII	1.92	1.99	2.54	1.81	2.41
Smoothed analysis	1.95	1.95	2.79	1.79	2.55
ORLA regression	2.04	1.94	2.75	1.73	2.56
Unadjusted rate	1.76	1.74	3.52	1.89	3.08

Source: Tables 2 and 8; Table 3 of Chapter IV-7.

TABLE 12.--SUMMARIES OF OVER-ALL DEATH RATES IN PERCENT

	Agent				
	H	N-B	C	E	O
Smoothed analysis	1.68	1.69	2.28	1:55	2.17
ORLA regression	1.71	1.68	2.32	1.62	2.17
Unadjusted	1.91	1.51	2.61	1.37	2.57

Source: Table 8; Table 1 of Chapter IV-2.

rate itself to be only 1 per 1560. How are these results to be reconciled? How can the difference between the death rates for halothane and cyclopropane be larger than the anesthetic death rate itself?

When there are multiple causes, it is difficult to assign responsibility with any definiteness. To say of a surgical death that it was an "anesthetic death," one must attribute the death to something very specific about the administration and the response to it in the particular patient. In their general capacity as catalysts for the success of an operation, some anesthetics may be slightly more successful than others, and the differences in death rates may not be due as much to active damage, as implied by the expression "anesthetic death," as to the general prevention of damage. However that may be, it is one thing to suggest that the identifiable occurrences of an event have a small rate, and a compatible but quite different thing to suggest that all actual occurrences of an event produce a larger rate; for example, we all recognize that the number of serious violators of traffic regulations is much larger than the number convicted. However, these differences may exaggerate the anesthetic effects because the adjustments rest on crude variables crudely grouped, because of sampling error, and because they include the effects of an observational study, rather than of an experiment.

Limitations on Generalizations

Population

Although the institutions participating in this Study do not come from a randomly constructed sample either of institutions or of patients in the United States, it is wise to think of the results as coming from some sampled population and to think of what kinds of hospitals are and are not represented.

As to types of hospitals among the 34: 15 are nonprofit corporations; three are church-affiliated; eight are state hospitals, two are county hospitals, and one is a city hospital; two are affiliated with the U.S. Air Force, one with the Veterans' Administration, and one with the U.S. Public Health Service; and one is hard to classify.

The institutions in the Study have from 250 to 1500 beds; the mean is 675 and the median is 650. Small hospitals are not represented in the sample, but nine have between 250 and 400 beds. Seven hospitals in the sample have over 1000 beds.

Obstetric uses of anesthetics were specifically excluded from the Study. Three of the hospitals are primarily for male patients.

With respect to age, the sample includes a children's hospital, a large hospital in a retirement area, and a hospital specializing in joint

diseases (which implies a predominance of older patients).

The hospitals joined the Study largely by volunteering when they heard of the plans for it, usually through NAS-NRC news or members. Service institutions were actively encouraged to join, but no attempt was made to publicize the Study on a national scale. Nevertheless, the geographic representation is broad.

All the hospitals have a teaching connection, and all have anesthesiologists. Compared with the nation's population of hospitals, the sample has heavy representation of hospitals with research interests, and especially research interests in anesthesiology. All the hospitals in the sample have records suitable for the Study.

Hospitals in which anesthesia is administered largely by nurses or other persons without medical degrees cannot regard the results of this Study as directly applicable to their practice of anesthesia. Possibly a study of a sample of small hospitals would be of interest.

Data

Data on the numbers of hospital deaths should be very sound. The weakness lies in the numbers of deaths that may have occurred outside the hospital within 6 weeks of operation, for these are not included. The careful investigation of this question appears expensive.

Although the recorded background variables may themselves often be in error for individual patients, for purposes of aggregative comparisons, such as we are making, they are likely to be, if not entirely satisfactory, at least a considerable improvement over making no adjustments at all. One special kind of weakness does exist in the rating of physical status. If physical status is assigned after the operation, rather than before, as may occur, then the adjustment for physical status is likely to correlate more highly with the outcome of the surgery than it would have if it had been assigned in advance. In such cases, the rating of physical status may explain too much and overadjust the death-rate differences between anesthetic agents, most likely leading to underestimation of those differences.

A few institutions or parts of institutions in this Study do not use the index of physical status, and the presence of this large clump of "unknown" has complicated the adjustments and to some extent reduced their effectiveness. If we were beginning the Study anew, we would reconsider the statistical treatment of the "unknown" group in the hope of strengthening the analysis.

We have attempted to defend against quirks of particular forms of analysis by executing several different kinds. Over-all, the results seem gratifyingly consistent.

Attention has repeatedly been called to the unreliable state of inferences about ether. Its distinctive pattern of institutional and operational usage has prevented our being able to reach any firm conclusion.

Objectivity of Planning and Analysis

In reflecting on how to achieve objectivity in such analyses as these, the statisticians noted that naming a study can have a considerable effect on its analysis. For example, this one was called the National Halothane Study. One effect of such a name is that it skews the interest in one direction and restricts, at least during the planning stage and the early analysis, the desirable equal scattering of attention that might have been implied by a less focused title, such as Comparative Study of Anesthetics. In at least one instance, the title of this Study led to a decision about what data to collect that made the final tabulations difficult to interpret. Fortunately, the magnitudes were all so small that it scarcely mattered, but the principle is as clear in a small mistake as in a big one.

Just as we use blindness to treatments in experimentation, there could be some advantage in blindness in the statistical analysis of the treatments under study through some definite stage. We realize that several difficulties face such a program; for example, certain comparisons would be made only between certain treatments, and in a large body of data certain treatments would identify themselves by their presence, absence, or known effects. On the other hand, we could go further than we have in the direction of blind analyses. One reason that blindness might matter concerns the intensity of follow-up. When a difference is observed that is unfavorable to one known treatment, the investigator may pursue it to the ends of the earth to try to explain it away, whereas the same difference unfavorable to another known treatment may be accepted with stoic indifference. Bias grows. The category "Other" partly illustrates this point in the present Study. Except for the overlapping analysis, no special study has been made to try to search out the reasons for the high death rates in this category, and it would be well if such a study were undertaken. At the same time, it is a study that could not itself be done very blindly, because of the hodgepodge nature of the category.

The study of Part IV is deliberately restricted to death rates. This restriction has the advantage of giving a rather definite criterion and of evaluating the over-all safety of halothane in terms comparable with those used in studying massive hepatic necrosis. Because small differences in death rates imply differences in numbers of deaths so much greater than those involved in massive hepatic necrosis, we can

say that the choice among anesthetic agents considered in this Study would almost always be made without consideration of deadly hepatic consequences. However, a weakness of the whole National Halothane Study is that it does attend especially to death as a criterion and does not consider explicitly other important factors of safety, comfort, ease, flexibility, and side effects, which the anesthetist must appraise. The anesthetist will find that, as far as the threat of death is concerned, this Study leaves halothane available as a free choice.

Finally, the National Halothane Study was a retrospective study and not an experiment. If it were desired to establish firmly the sizes of differences between the death rates associated with the anesthetic agents when used on comparable patients, a large experiment would be required.

INSTITUTIONAL DIFFERENCES

Death rates for the 6-week period after surgery varied widely among the 34 institutions cooperating in this Study. They ranged from 0.0027 to 0.0640, a 24-fold ratio. In six institutions, the death rate was below 0.0100; in 10, it was above 0.0300. Such variation in so important an outcome of surgery compels attention.

It was clear from the beginning that some, possibly large, variation in institutional death rates would be a necessary consequence of the institutions' varied patient populations, surgical loads, etc. So the institutions' death rates were adjusted separately for each of the variables sex, year, previous operation, physical status, age, operation, and SLI. The first three had no appreciable effect, but adjustment for each of the remaining variables substantially reduced the heterogeneity of institutional death rates; the original 24-fold variation came down to about 10-fold with each of the last three. Multiple adjustment for age, operation, and physical status reduced the extreme ratio to about 3 for the middle-death-rate operations only.

Thus, there is evidence that a large part of the variation in institutional death rates is attributable to differences in age distribution of patients, to differences in the frequency with which high-risk and difficult operations are undertaken, and to the balance between elective and emergency procedures. Moreover, we can be nearly sure that fully adequate allowance for these factors would reduce the apparent hospital variation further, but we cannot say how much.

There do remain, after all the analyses we have seen fit to apply, substantial differences in adjusted institutional death rates. We must face several questions concerning them:

(1) Are the differences large enough, compared with sampling error, to call for explanation as other than plausibly random irregularities? (Are the differences real?)
(2) If they do outweigh sampling error enough to be "real," what do they mean? Are they evidence of "excess" deaths?
(3) How important are the deaths quantitatively? Are thousands, hundreds, or dozens of deaths involved?
(4) If the reality of the differences is accepted, their meaning is understood, and they are quantitatively large, what are the reasonable indications for further study or action? The answer to this difficult question must be well proportioned to administrative and legal (and emotional) realities, as well as to medical-scientific and statistical factors.

To get a more direct grasp on the question of the reality of the differences, we chose six operations (as described in Chapter IV-6) that were common in nearly all the hospitals, and studied the death rates for merely those six (about 16 percent of the data). No elaborate adjustments were made. Strikingly, the institutions with the highest death rates (unadjusted) for the six chosen operations agreed well with the institutions that gave the strongest appearance of being "high" on the middle-death-rate operations after multiple adjustments. The evidence for "real" institutional differences on the six operations is very strong. We conclude that there are real differences in institutional death rates that are explained neither by the data taken in the Study (age, sex, physical status, operation, etc.) nor by sampling error.

Some of the institutions had surgical deaths far outweighing the standard value ascribed to them by our statistical methods. In any such case, this may mean that deaths are high, or that the standard value is low. The latter possibility could arise because statistical adjustments have corrected inadequately for age, operation, etc., because they have taken no account of other important institutional properties, or both. Sometimes statistical adjustments for interfering variables tend to undercorrect, and Appendix 2 to Chapter IV-6 gives strong evidence of an important tendency of this kind in some of our data. Furthermore, it is true that many variables relevant to surgical death rates have not been studied, and data have not been taken on them. Such variables include the general nutritional and health level of the institutions' clienteles, the willingness of the institutions' staffs to undertake risky cases, and the tendency of the institutions to be sent (and to accept) a high fraction of problem cases. Accordingly, we must recognize that if an institution seems "high" in our data (with statistical significance), we are not able to conclude that its surgical

death rate is therefore "excessive." But the question is certain even if the answer is not.

Gauging the quantitative importance of the institutional differences is partly a matter of observing that in several institutions actual deaths exceeded a calculated standard for the institution by more than 200. Indeed, the sum of all "excesses" was about 1750 for the middle- and high-death-rate operations. However, institutions with favorable experience had an aggregate sum of 1750 fewer deaths in the middle- and high-death-rate operations than the calculated standards for those institutions. The total number of deaths in the study was about 17,000; thus, positive and negative swings of 1750 are not to be ignored. More importantly, the main portions of these sums came from a very few institutions: about half the "excesses" came from three institutions, and about half the "deficits" from three.

This tendency for the major part of the unexplained differences to be concentrated in a few places improves the prospects of being able to "do" something, such as to understand what actualities underlie the observed statistics or, possibly, even to identify opportunities for useful action. In assessing the quantitative importance of the heterogeneity of adjusted death rates, it would not only be good to know that institutions x, y, and z had unexplained high death rates, but far more important to know whether these institutions were representative of 1, 5, 10, or 20 percent of hospital practice in the United States. The larger the group they "represent," the greater the quantitative importance attaching to the elucidation of their death-rate experience. Unfortunately, this question of representation is not one on which reliable information can be given.

If we accept the unexplained differences as "real," and regard the magnitudes as definitely important, we come to the last issue: what to do? The problem is difficult. First, it must be recognized that we do not know for sure which institutions (if any) are the right ones to study. It is true that our evidence for the existence of real unexplained differences in institutional death rates has been the occurrence of several death rates that appear to be "outliers" in our data, but some of these may have resulted from large random fluctuations, and, similarly, some others deserving study may not have appeared in our sample as definitely high. Second, not only do we not know for sure which institutions should be studied, but we do not have from the statistical study any clear idea of what kinds of things should be studied. Finally, many important and delicate questions must be faced if a useful study of so challenging a question ("Are there many preventable deaths in this institution?") is to be possible.

Thus, although we are persuaded by the evidence that some institutions have higher death rates than others, even after adjustment for the variables on which we have data, we are not persuaded that "strenuous efforts to correct the situation" are necessarily called for. With ill-defined targets for study and so sensitive an issue to explore, it would be all too easy to set in motion what could fairly be called a circus.

At the same time, indications of such importance based on so many data should not be swept under the rug. We feel that, at a minimum, "someone" should recognize that there may be a problem and that it is not trivial. "Someone" should try to ascertain which institutions, although inexplicable by our data, are readily understood as "naturally" having high death rates because of, for example, the poverty of their clientele, or other compelling and well-understood reasons.

Finally, "someone," after finding a remaining set of hospitals whose death-rate experience cannot be dismissed, should cause these to be thought about. Quiet, unofficial, cooperatively oriented inquiries into opportunities for studying the problems should be sought. Perhaps two hospitals, comparable except for death-rate experience, could exchange two or three members of their staffs for a period of a year, for instance. Perhaps a cooperative, randomized trial of anesthetics on one or two operations (included in our set of six) would afford an opportunity for communication and exchange of experience that would lead to better understanding and improved practice. The importance of corrective efforts arises not from their effects (if successful) in these hospitals, but from the benefits that may accrue by wider application of similar efforts later.

In summary, real and important differences in death rates do exist. They are not explainable statistically. Explanation will have to rest on medical-social-biologic procedural information. Getting the relevant understanding will be difficult. The effects chosen for study will have to be large if the hope of useful results is to be more than slight.

METHODOLOGY

Randomized Trials versus Study of Past Data

In discussing the design of an investigation like the National Halothane Study, one's first thought is that the natural and firm study will assign patients to their treatment groups on a random basis. Yet, the National Halothane Study used past data. Consequently, in Chapter II-1 reasons for studying past data were reviewed, together with the liabilities of the method. In addition, views about these pro's and con's in the light of the study performed may be helpful, even though the writers, as participants, are inevitably somewhat biased.

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The greatest merit of the randomized clinical trial is its natural defense against sources of bias that cannot be recorded or perhaps even imagined. Its over-all results could be analyzed by straightforward statistical methods (for such purposes as comparing over-all death rates). But the importance of confirming over-all comparisons within each of as many groups as possible increases the desirability of gaining precision. To get increased precision, then, it might well be important to make computations of the kind and complexity undertaken in the present retrospective study, even if the data were drawn from a randomized trial.

In the randomized study, there is a great risk that such a trial may collapse under ethical challenge and be a total loss. As it has turned out, ethical challenges can now be met by extensive data; indeed, the whole problem is quite different in the light of the study of the retrospective data, for halothane now looks safer than cyclopropane.

In a randomized trial, it might well have been possible, although expensive, at least in parts of the study, to trace patients leaving the hospital within the standard 6-week period so as to study all deaths, rather than only those that occurred in the hospitals. In the study of hepatic necrosis, however, even the randomized clinical trial would have had no way of ensuring that a high rate of complete necropsy could be obtained; therefore, that part of the study would still be subject to a very large rate of nonresponse. (There may also be problems about differential ability to rate the necrosis at different times between death and necropsy.) Unless this nonresponse rate can be reduced, perhaps through biopsy if full necropsy is not feasible, the more controlled trial may not be worth carrying out as a means of studying massive hepatic necrosis.

It seemed valuable to get historical data on death rates. Indeed, the design of a randomized trial of any two anesthetics might be aided by a careful study of a breakdown of the data on operative procedures by institution, anesthetic, and operation, together with the corresponding death rates. This would help in selecting operations for which choice of anesthetic might make a measurable difference and for which alternatives were clearly available. Of course, these historical data also offer baselines against which surgical teams and hospitals can measure their performance and improvement.

When one recalls that the evidence against halothane was small, compared with the excellence of its reputation and the extent of the studies in its favor, the reluctance to set up a large, long, expensive study becomes clearer, particularly inasmuch as the original fears might well be settled by a study of past data.

Because a randomized trial was not done, it is hard to say what it would have been like, but at one time a study comparable in size with the study actually done was under consideration. It might have required 4 or 5 years for the data-gathering process alone. The expense in money and professional talent would have been considerably greater, as would the demands on the participating hospitals. Similarly, the staff of the central office would have had to be larger and would have had to participate more continuously in traveling and monitoring operations. In retrospect, considering the effort and training that went into the making of the team that carried out the several phases of the simpler study of past data, some Committee members believe that even the preparatory stage for a randomized clinical trial would have taken an additional year.

These remarks merely describe a specific shortcoming of our national medical research picture, one emphasized by Wilfrid Dixon in discussing with us the problems of large-scale, cooperative, randomized trials. He pointed out that good will and hard work, although necessary, are no substitutes for a trained team of medical research workers, statisticians, data analysts, and processors, including scientific administrators and finance experts. Dixon pointed out that few such teams exist, that few persons realize how long it takes to train one, and that in this country we do not yet systematically try to produce such teams and keep them organized. Seen from that point of view, the National Halothane Study certainly had no such team to start with, and at its close had only a partial capability of handling a large, cooperative, randomized trial--a partial capability now largely dispersed. In an era of increased governmental support for medicine and increasingly frequent searches for rare occurrences, the notion of building and maintaining such teams should become more important. If a program for building and maintaining such teams is developed, it should make the execution of randomized trials much more feasible. The existence of such teams might facilitate the more systematic evaluation of new drugs and therapies.

Because the rates of usage of the several anesthetic agents varied greatly from one hospital to another, something other than simply careful choice appropriate to individual patients was behind the usage rates. Either policy or personal preference must have ruled many of the decisions. This fact weakens somewhat the argument against the study of past data that claims that each anesthetic agent was especially chosen from among all agents to be optimum for each patient and his operation. We have used hospitals in which comparison was possible to get more comparative data on anesthetics. These data support further the general findings of the Study. Ironically, but inevitably, it is in the hospitals in which direct comparison is possible that the argument for possible selection biases by the anesthetist is hardest to combat.

This discussion is intended, not to deprecate the randomized trial, but rather to set

forth the view that it is not the only tool useful to the investigator with a question relating to the comparison of therapies. Finally, as discussed in Chapter IV-1, very small differences may be unresolvable by any method, for the very actions required to set up a randomized trial may change the effect that was to be measured.

Data Analysis

The key problem from the point of view of applying existing methods of statistical analysis was that the complete cross-classification natural to the data had so many cells, compared with the number of cases, that most cells had poorly determined death rates. To handle this difficulty, several new methods of analyzing data from multidimensional contingency tables (or even from continuous variables if no harm comes from grouping them) were used. Two basic problems have been treated: (1) getting estimates for counts or rates in cells determined by several variables, and (2) getting summary statistics over the entire set of data to make over-all comparisons. Both problems need treatment in many studies--not only in such fields as medicine and biology, but wherever contingency tables arise, and especially in the social sciences.

The smoothed contingency-table analysis was especially designed to obtain improved cell estimates by borrowing strength from the margins of the table, not only from single-factor margins, but also from those of higher dimension. To get such improvements, something had to be given up, and it is the simultaneous effects of four or more variables that have been sacrificed here. The simultaneous effects of all possible sets of three variables from among those included in the investigation have often been retained. In other instances, the data were fitted satisfactorily by retaining only the information about pairs of variables.

Multiple regression is a device for estimating cell values, but it was not used for this primary purpose in this Study. Instead, the calculation of regression values led to the construction of strata used in computing summary statistics for the whole Study.

Cell aggregation methods are used for grouping cells homogeneous on the key variable (here, death rates) so as to improve the reliability of over-all statistics. These methods can be applied in many different ways. For example, in the smoothed contingency-table analysis we fitted the death rates in the cells without including the variable "anesthetic agent," and then grouped cells by the fitted death rates so as to collect more cases for basic rates. Rates according to the separate agents were then computed within the aggregated cells, and finally these were applied to some standard population to get summary statistics for the whole Study.

Smear-and-sweep (Chapter IV-4) uses regression to borrow strength in making cell estimates preliminary to sweeping (aggregating) the cells of a two-way array into one new pseudo-variable. These cell estimates then guide the cell aggregation so that homogeneous cells are collected together, just as in the regression method (Chapter IV-5). However, the pseudo-variable may be used to form an additional array, by smearing each cell of the pseudo-variable along the distribution of values of the new variable for cases in the cell. This smearing produces a new two-way array. Then a new regression is computed and a new cell aggregation is performed to form a new pseudo-variable, and so on. In the end, a set of summary statistics is computed.

A new method, superstandardization, of appraising incompleteness of the adjustments has been described in Appendix 2 to Chapter IV-6.

Because the estimation of cell values and the computation of summary statistics are common and important problems, these methods may find themselves in much wider use in the future. Naturally, owing to their newness, they will produce many theoretical problems for statistical research workers.

CONCLUSIONS AND RECOMMENDATIONS FROM THE STUDY OF DEATH RATES

(1) Halothane, rather than being a dangerous anesthetic, appears to have a lower death rate than either cyclopropane or Other, and to have a rate about equal to that of nitrous oxide-barbiturate for many classes of operation, including the more severe ones.

(2) Cyclopropane, even after adjustment (undoubtedly incomplete) for interfering variables, shows a higher death rate than halothane in the middle-death-rate operations, and the differences may be even larger in the high-death-rate operations.

(3) The performance of ether poses an important puzzle. It has an excellent record in a few hospitals, but our assessment is unreliable.

(4) The mixed category of anesthetics, Other, corresponds to a higher death rate than halothane or nitrous oxide-barbiturate. This finding is difficult to interpret, partly because of the large number of anesthetics and combinations included in this category. Insofar as we can tell, halothane, nitrous oxide-barbiturate, ether, and their combinations have had a much better record than the less-used anesthetics and their combinations.

(5) Institutional differences in death rates may be large enough, even after allowance for

age, operation, and physical status, to suggest the need for studies of the sources of these differences. However, the administrative, economic, social, legal, and medical problems in embarking on such a large study with such a diffuse target hold us back from making a definitive recommendation. The matter should be considered carefully and an alert watch kept for any natural opportunities that would make such a venture more likely to succeed than it appears to be at the moment. The existence of obvious differences in the background of patient populations--e.g., level of nutrition--and differences in institutional personnel and budget may already be enough to account for much of the variation that our data do not explain, and little in this Study allows for these variables.

(6) New consideration should be given to building teams of medical research workers (adequately advised and supported in both statistics and data analysis) for carrying out large cooperative studies. In addition, more effective and more frequently used mechanisms should be developed for evaluating, particularly through large-scale cooperative trials, new therapies during their early years of clinical use.

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PART V. THE TOXICOLOGY OF DICHLOROHEXAFLUOROBUTENE

PART V. THE TOXICOLOGY OF DICHLOROHEXAFLUOROBUTENE

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The synthesis of 2,3-dichloro-1,1,1,4,4,4-[hexafluorobutene-2 was first described by Henne et al. in 1945 (4). Lu and his associates in an earlier study had published a brief report on the toxic effects of dichlorohexafluorobutene (DCHFB) in the rat (5), but the compound evoked little medical interest until 1963, when it was isolated as an impurity in the anesthetic halothane (Fluothane), and its toxicity was confirmed in both the rat and the dog (1).

Soon after the introduction of halothane into clinical practice (1958 in the United States), a small but increasing number of disturbing case reports appeared, suggesting a possible relationship between halothane and hepatic necrosis (see Chapter I-3). The isolation, in 1963, of a potentially toxic contaminant in halothane led to the suspicion that this material might be responsible for the hepatic necrosis attributed to halothane. Accordingly, under the auspices of the National Halothane Study, a detailed investigation of the toxicology of DCHFB was begun in 1963 and completed the following year.

It has not been possible to confirm or deny a cause-and-effect relationship between inhalation of DCHFB and hepatic necrosis in man. Studies of toxicity in animals cannot be directly extrapolated to man. The retrospective study reported herein was not designed to compare the effects of butene-contaminated and butene-free halothane, and a prospective study involving administration of such a potentially toxic material (butene-contaminated halothane) to man was out of the question. For these reasons, it is unlikely that this question can ever be completely resolved.

The DCHFB in halothane is a byproduct of manufacture. At the time of the Study, halothane was prepared in this country and in England by a process of exchange halogenation at high temperature, or by direct bromination of CF_3CH_2Cl. Both processes resulted in traces of cis- and trans-DCHFB, as well as several other impurities (Fig. 1).

By gas chromatographic analysis, the concentration of "butene" in stock halothane was found to be approximately 180 ppm (2). Further evidence at that time indicated that this contaminant was found in increased concentrations under conditions of anesthetic administration. The exact limit of this increase has been the subject of several investigations. In two studies totaling 183 individual analyses (2,8), the mean concentration of DCHFB found in anesthetic vaporizers was 29 to 300 ppm. A third study reported the initial concentration of DCHFB (the trans-isomer only) to be 350 ppm in stock halothane (6), but only slight changes in concentration were observed in eight anesthetic vaporizers over an 8-week period. Sexton and his associates (8) reported a DCHFB concentration of 580 ppm in material taken from one vaporizer, and Cohen and his associates (1) reported 1000 ppm in another sample. These higher concentrations were the exception, rather than the rule. It was suggested that the increased concentration of DCHFB resulted from a selective evaporation of the more volatile halothane, as well as from an interaction between halothane and copper (Fig. 2) (2). The suggested role of copper vaporizers in producing this increase remains unconfirmed.

A number of toxicologic studies have been carried out with DCHFB in the experimental animal. Studies by Torkelson and Chenoweth (9), Corrigan et al. (3), Cohen et al. (2), and Raventos and Lemon (7) are in agreement that DCHFB is highly toxic to each of the animal species investigated (mouse, rat, rabbit, dog, and monkey). There does not appear to be a uniformity in response among the various species, although one finds a dose-effect relationship in determining the LC_{50}. In the mouse, for example, an LC_{50} of 55 ppm for 1 hr of inhalation decreased to 20 ppm by 6 hr (7). The species most sensitive to DCHFB is the rabbit, and the dog appears to be the most resistant. The mouse, rat, and monkey show an intermediate sensitivity. In the monkey, the LC_{50} has been reported as 54-90 ppm after a 3-hr exposure. Table 1 presents the combined data on LC_{50} from several studies (2,3,7).

TABLE 1.--THE LC_{50} of DCHFB

Species	LC_{50}, ppm by inhalation		
	1 hr	3 hr	6 hr
Mouse	55	-	20
Rat	47	28	16
Rabbit	30-40	-	-
Dog	725	200	115
Monkey	186	54-90	-

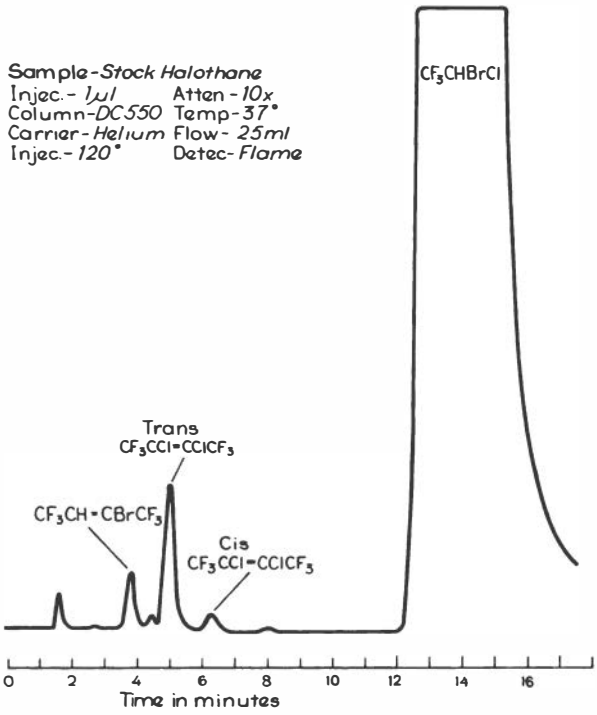

Figure 1.--Chromatogram obtained from the injection of 1µl of stock halothane (Ayerst Laboratories, Lot D7892HF). (Figures 1 through 5 from Cohen, E. N., H. W. Brewer, J. W. Bellville, and R. Sher. The chemistry and toxicology of dichlorohexafluorobutene. Anesthesiology 26:140-153, 1965. Reprinted with permission.)

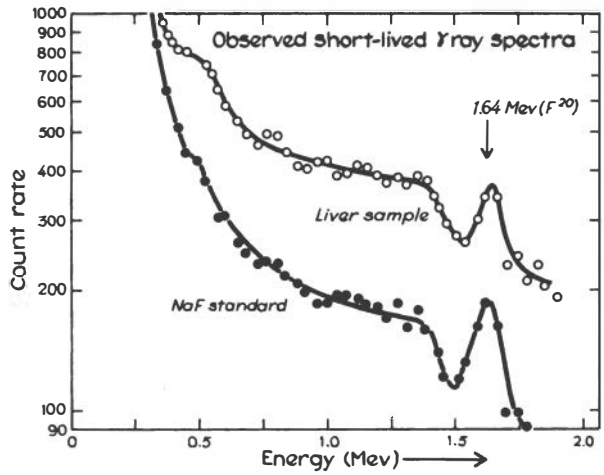

Figure 3.--Gamma ray spectrum obtained by irradiation of NaF standard and liver tissue in area of low neutron flux. Animal exposed to 0.3 percent DCHFB inhalation for 60 min. In both samples, 1.64-Mev peak represents F^{20}.

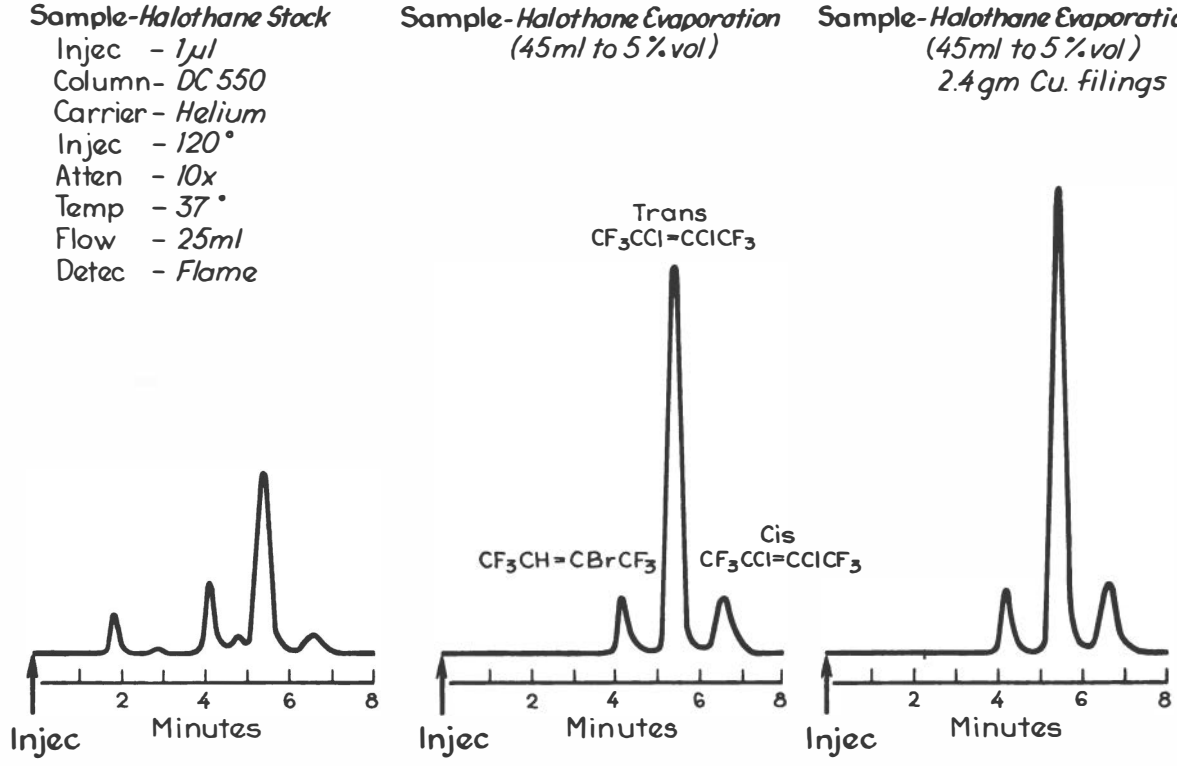

Figure 2.--Chromatographic tracings contrasting the effects of evaporation alone, and evaporation combined with copper. Evaporation of halothane for 72 hr at room temperature in original container.

It cannot be assumed that, because the LC_{50} in animals is higher than those concentrations usually attained under clinical conditions, any danger can be disregarded. If an average concentration of DCHFB in the anesthetic vaporizer is 300 ppm, and if halothane is administered in a concentration of 1 to 2 percent, an alveolar concentration of butene as high as 6 ppm might be expected, representing a safety factor of only 5 to 10 in relation to the LC_{50} found in most animal species, including the monkey. The administration to man of concentrations close to those which are toxic to animals must be considered hazardous, particularly if one considers the possibility that variations in sensitivity may, for example, place 6 ppm within an "LC_{01}."

The considerable species variation in toxic effects of DCHFB further complicates clinical interpretation. In all animals, inhalation of "butene" produces an intense pulmonary irritation, with congestion, edema, exudation, and consolidation. Cohen and his associates (2) showed the dog's lung to be very resistant, although Raventos and Lemon (7) were able to produce severe lung damage in dogs with a high butene concentration. Pathologic changes in the kidneys were found in the rat (7) and in the dog (2), and included small thromboses in the glomerular capillaries with degenerative changes in the renal tubules.

Of special interest to the National Halothane Study are the pathologic changes found in the liver after inhalation of DCHFB. Although Torkelson and Chenoweth (9) and Cohen et al (2), were able to demonstrate hepatic damage in the rat (in severe cases, central lobular necrosis), Raventos and Lemon (7) found only "congested livers" in this species. Similarly, the latter workers described a "mild central lobular degeneration" in the monkey (3), and Cohen and his associates (2) found in the same species fatty degeneration of the liver, and central lobular necrosis in the more severe cases. The contributory role of hypoxia in association with the pulmonary toxicity may be an additive factor, although Torkelson and Chenoweth (9) reported hepatic damage in rats after the oral gavage of DCHFB.

Studies of the uptake and distribution of DCHFB (2) are pertinent. These have been carried out primarily in the monkey, and a few observations have been made in man. Following inhalation in the monkey of 0.1 percent butene for 60 min, the highest concentrations of DCHFB were measured in the rapidly perfused organs of the body (kidney, brain, and adrenal), but with the notable exception of the liver. Calculations of hepatic clearance for DCHFB in the monkey indicate that 110 μg/kg are cleared per minute at an inhaled concentration of 0.1 percent. Despite these clearance rates, DCHFB could not be demonstrated in hepatic samples surgically removed and analyzed by gas chromatography. This implies that DCHFB no longer was present within the liver in its original chemical state, inasmuch as DCHFB concentrations of one part in 10 million could readily be detected in other tissues by means of electron capture gas chromatography. Evidence of the metabolism of DCHFB by the liver has been found with activation analysis techniques (2). Demonstration of a fluorinated product in the liver, not present before the administration of DCHFB, indicates a metabolite of butene as the source (Fig. 3).

Studies of the uptake of butene in man have been limited to the trace concentrations of DCHFB already present in commercial halothane (2). In a study of five patients, 1 percent halothane was administered in a nonrebreathing system; analysis of inhaled and exhaled concentrations of DCHFB indicated maintenance of a steady 5 to 10 percent gradient, thus providing evidence of the alveolar uptake of butene (Fig. 4). These observations were in agreement with an analogue simulation of the uptake of butene, based on its known physical properties (2).

A second study of five patients was performed with the inhaled concentration of halothane set at 1 percent, but the rebreathing system was now completely closed and only enough oxygen added to the system to meet metabolic needs (2). The halothane concentration delivered to the patients was kept at 1 percent by adjusting the gas fraction flowing through the vaporizer and monitoring the inhaled concentration with an ultraviolet meter. Despite the known lower blood solubility of DCHFB than of halothane, there was a falling concentration of DCHFB in the inspired concentration. This observation is consistent with the suggested metabolism of DCHFB (Fig. 5).

On the basis of the animal experiments conducted in association with the National Halothane Study, it was recommended that DCHFB be removed from halothane. This suggestion was adopted by the manufacturer, and the halothane now used in the United States is essentially free of this contaminant. The present commercial product contains 5 ppm or less (2,7). Thus, from a practical point of view, the hazard no longer exists.

In summary, DCHFB is a contaminant of halothane manufactured at high temperatures, and its presence has been demonstrated in stock halothane. It has also been found clinically in increased concentration in anesthetic vaporizers, but not consistently. When halothane is administered, DCHFB is simultaneously vaporized and taken up in animal and man. It has proved toxic to all animals tested, and the determined LC_{50}'s are close to the concentrations actually administered to man. Although DCHFB produces hepatic damage in some animals, a direct cause-and-effect relationship between DCHFB and halothane hepatic necrosis in man remains unproved. Despite some species variations in toxicology, the presence of butene in halothane, even in trace amounts, represented a potential danger during the clinical administration of this anesthetic agent, and the manufacturer has properly eliminated it.

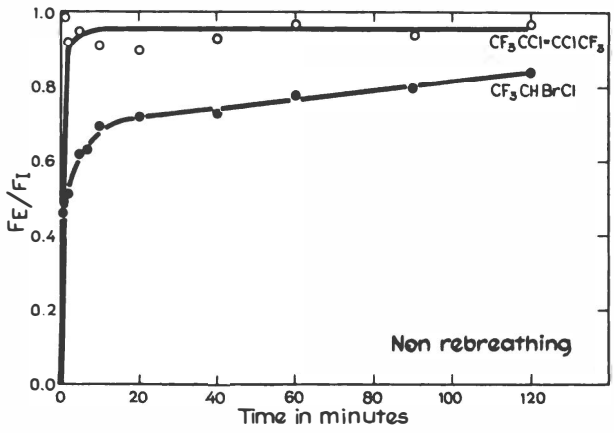

Figure 4.--Uptake of DCHFB compared with halothane in a nonrebreathing system. Inhalation of halothane maintained at constant concentration. Note rapidly rising concentration of DCHFB in exhaled alveolar gas.

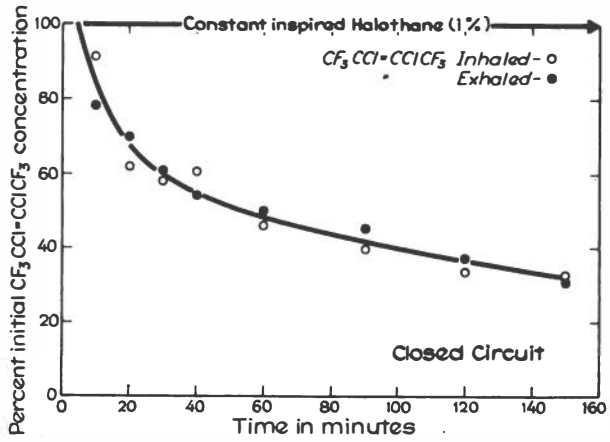

Figure 5.--Uptake of DCHFB in closed-circuit system. Note falling concentration of inhaled and exhaled DCHFB despite its lower solubility in blood. Data represent percentage reduction from initial peak concentration.

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PART VI. FORMAL RECOMMENDATIONS

PART VI. FORMAL RECOMMENDATIONS

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Although this report might make it appear as though there were two separate studies (hepatic necrosis and surgical death rates), it should be emphasized that the Subcommittee, ably supported by its consultants, worked as a single remarkably harmonious team, and that all major decisions in the design and implementation of the Study were made by the full Subcommittee.

The final action of the Subcommittee, taken early in 1966, was to formulate a series of recommendations, which it was hoped might be of special interest and importance to the practice and science of medicine. Four recommendations were agreed on, of which three appear below.

The fourth called for the implementation of studies of the marked variability in reported death rate from one institution to another. This recommendation was withdrawn from the summary report (1) because of the difficulties in appraising and interpreting the observed differences; but the possibility was left open that further analyses could lead in this full report to a new recommendation for studying institutional variation. Further analyses were carried out (Chapter IV-6), and their implications are discussed at length in Chapter IV-8, where the original recommendation is tentatively reintroduced.

The personal recommendations of Lincoln E. Moses and Frederick Mosteller, that new consideration be given to building teams of medical research workers for carrying out large cooperative studies and that new mechanisms be developed for evaluating, particularly through large-scale cooperative trials, new therapies that have passed the developmental stage, also appear in Chapter IV-8. Their proposals are closely related to the Subcommittee's Recommendation 2.

Attention should also be called to Chapter III-5, in which two members of the Subcommittee suggest how the results of the Study might be applied to the practice of anesthesia. This they do with some hesitation, for each physician should, and will, draw his own conclusions and apply them to his practice of medicine as he sees fit.

Here, then, are the formal recommendations of the Subcommittee on the National Halothane Study:

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

The present Study has provided baseline data on death rates and 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 with other uses of medical resources, it is thought worth while 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 that 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 percent; (3) the operation is one that is frequently performed; and (4) necropsy rates can be anticipated to be sufficiently high if necropsies are needed to ensure 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 after operations 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 questions of nonfatal hepatic 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 halothane been administered a few scores of thousands of times 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 over-all death rates, and possibly for nonfatal hepatic injury as well.

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

Massive hepatic necrosis is rare, but usually fatal. In some patients it follows what appears to be typical viral hepatitis. Massive hepatic necrosis may also follow some 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 to be perhaps 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 the kind of panel mentioned in Recommendation 2, 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; and (3) the loss of data by nonresponse, such as missing laboratory data and failure to obtain necropsy. In addition, other, possibly serious, difficulties will undoubtedly 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. On 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.

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