United States
Environmental Protection
Agency

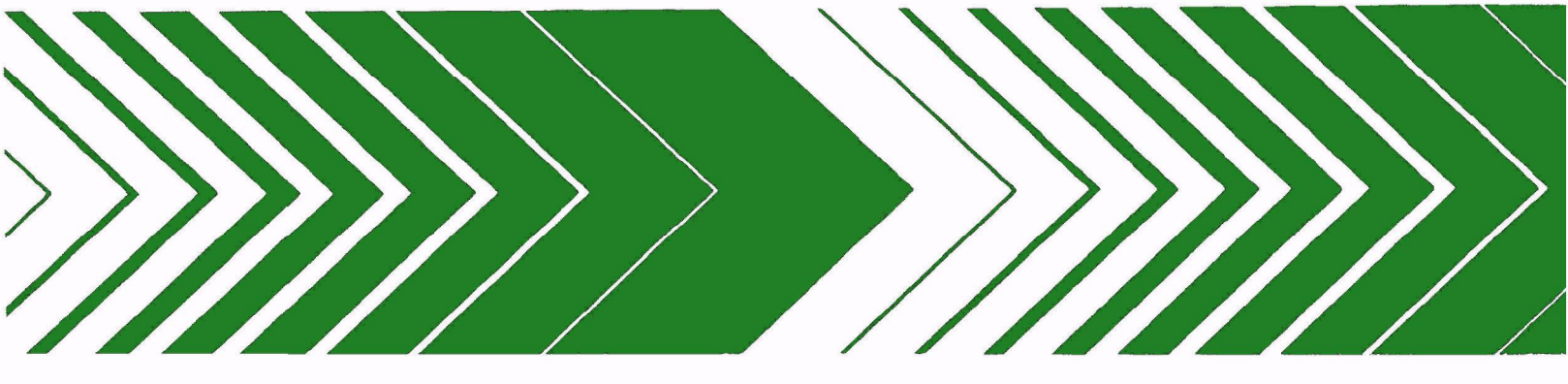
Health Effects Research
Laboratory
Cincinnati OH 45268

EPA-600/1-79-043
October 1979

Research and Development

EPA

Causes of Death of Anesthesiologists from the Chloroform Era



RESEARCH REPORTING SERIES

Research reports of the Office of Research and Development, U.S. Environmental Protection Agency, have been grouped into nine series. These nine broad categories were established to facilitate further development and application of environmental technology. Elimination of traditional grouping was consciously planned to foster technology transfer and a maximum interface in related fields. The nine series are:

1. Environmental Health Effects Research
2. Environmental Protection Technology
3. Ecological Research
4. Environmental Monitoring
5. Socioeconomic Environmental Studies
6. Scientific and Technical Assessment Reports (STAR)
7. Interagency Energy-Environment Research and Development
8. "Special" Reports
9. Miscellaneous Reports

This report has been assigned to the ENVIRONMENTAL HEALTH EFFECTS RESEARCH series. This series describes projects and studies relating to the tolerances of man for unhealthful substances or conditions. This work is generally assessed from a medical viewpoint, including physiological or psychological studies. In addition to toxicology and other medical specialities, study areas include biomedical instrumentation and health research techniques utilizing animals — but always with intended application to human health measures.

This document is available to the public through the National Technical Information Service, Springfield, Virginia 22161.

EPA-600/1-79-043
October 1979

CAUSES OF DEATH OF ANESTHESIOLOGISTS FROM THE CHLOROFORM ERA

by

Harry W. Linde
and
Paul S. Mesnick
Northwestern University
Chicago, Illinois 60611

Grant No. R805473-01

Project Officer

James B. Lucas
Health Effects Research Laboratory
Cincinnati, Ohio 45268

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OHIO 45268

DISCLAIMER

This report has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the U.S. Environmental Protection Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

FOREWORD

The U.S. Environmental Protection Agency was created because of increasing public and government concern about the dangers of pollution to the health and welfare of the American people. Noxious air, foul water, and spoiled land are tragic testimony to the deterioration of our national environment. The complexity of that environment and the interplay between its components require a concentrated and integrated attack on the problem.

Research and development is that necessary first step in problem solutions. The primary mission of the Health Effects Research Laboratory in Cincinnati (HERL) is to provide a sound health effects data base in support of the regulatory activities of the EPA. To this end, HERL conducts a research program to identify, characterize, and quantitate harmful effects of pollutants that may result from exposure to chemical, physical, or biological agents found in the environment. In addition to the valuable health information generated by these activities, new research techniques and methods are being developed that contribute to a better understanding of human biochemical and physiological functions, and how these functions are altered by low-level insults.

This report is one in a series undertaken to assess the potential health impact of chloroform, the major by-product of chlorine disinfection of water supplies. Such research provides a basis for decisions by the Administrator regarding the necessity for modifying current drinking water treatment practices. Through a better understanding of health effects, measures can be taken to reduce exposures to potentially harmful substances.

R.J. Garner
Director
Health Effects Research Laboratory

ABSTRACT

This investigation was undertaken to determine if there were an excess of cancer deaths occurring in anesthesiologists who practiced in an era when chloroform was in use and to estimate the degree of chloroform usage during that era. Causes of death of anesthesiologists dying between 1930 and 1946 were determined. They were presumed to have been in practice as early as 1880-1890 when chloroform was one of the two most widely used anesthetic vapors.

Names of white male anesthesiologists listed in directories for 1930-1946 were searched in the death files of the American Medical Association. A total of 274 deaths occurred among those listed. Copies of death certificates were obtained from vital statistics offices to ascertain the cause of death. Death from cancer occurred in 31 cases (11.3% of deaths), from cardiovascular diseases, 173 (63.1%), from accidents and suicides, 20 (7.3%), from infection, 20 (7.3%) and from all other causes 30 (10.9%). It was not possible to find a cause of death in 5 cases.

Death rates in this group of anesthesiologists were compared to rates for U.S. white males, male physicians, anesthesiologists in later decades, and life insurance policyholders. Combined death rates were lower among anesthesiologists than the U.S. male population but exceeded them for some cardiovascular diseases. Death rates for combined malignant neoplasms were low, with digestive organ neoplasms being the most common. Death rates from malignancies of the respiratory tract were unusually low. The cardiovascular disease death rate was similar to that for anesthesiologists in the next decade although there were fewer deaths from cerebrovascular accidents and more from heart disease. Death rates for all malignant neoplasms dropped by about one-fifth over the subsequent two decades.

Review of the literature suggests that chloroform was used for about two-thirds of all anesthetics in England in 1890, dropping to about one-half by 1920 and to about zero by 1950. Overall use of chloroform in the United States appears to have been similar at first then lower, especially in the later years, although there was considerable regional variation in its use with some hospitals having rates similar to those in England.

Anesthesiologists in the United States in the late 19th and early 20th centuries appear to have been occupationally-exposed to chloroform vapor. Their death rates from all malignant neoplasms and from those of the digestive organs are somewhat greater than for anesthesiologists several decades later. No firm conclusions on carcinogenesis can be drawn, however, because of the small population and small number of deaths involved and the different age distributions of the groups of anesthesiologists.

This report was submitted in fulfillment of grant R805473-01 by Northwestern University under the sponsorship of the U.S. Environmental Protection Agency. This report covers a period from January 1, 1930 to December 31, 1946, and work was completed as of March 31, 1979.

CONTENTS

TABLES

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the assistance of the following:

Norbert J. Smith, Research Associate, Statistical Bureau, Metropolitan Life Insurance Company for providing statistical advice and consultation and mortality tables.

The American Society of Anesthesiologists and the Wood Library and Museum for making available old records and minutes of the society, and Patrick Sim, Librarian.

The American Medical Association for making available their death records for study and Ms. Victoria Bigelow, Research Associate, Division of Library and Archival Services.

David L. Bruce, M.D. for assistance in design of the study, access to his unpublished data from previous studies and consultation.

Thomas H. Seldon, M.D. for providing old directories of the International Anesthesia Research Society.

The Offices of Vital Statistics of the states and New York City.

Mrs. Karen McGary, Mrs. Shelia Brown and Ms. Rita Schwimmer who assisted in collecting and collating data.

INTRODUCTION

Chloroform has been implicated as an animal carcinogen (1). The effect of chloroform on man is of interest since it has been found in small quantities in some drinking water supplies and is used as a solvent in industry and in the laboratory. Chloroform was introduced in 1847 as an inhalation anesthetic agent and was used for this purpose during the latter half of the 19th century and into the 20th century. With the recognition of its side effects, and with the introduction of newer and safer drugs, the use of chloroform declined, so that by the mid 20th century, it was rarely used for this purpose. Anesthesiologists* who administered chloroform were inevitably exposed to its vapors in sub-anesthetic concentration while the drug was being used. If we consider anesthesiologists dying between 1930 and 1946 at an average age of 65 years and after 40 years of practice, they would have given anesthetics between 1890 and 1946, during much of the chloroform era. If chloroform did exert long-term toxic effects, e.g. carcinogenesis, then it would seem likely that mortality statistics for a group of anesthesiologists would reflect this toxicity.

This study was undertaken to identify a population of anesthesiologists who were likely to have used chloroform, to determine the causes of death of those who died during the years 1930 to 1946 and to examine these mortality statistics by comparison with other groups. An additional objective was to assess the relative usage of chloroform for anesthesia in the late 19th and early 20th centuries.

CONCLUSIONS

Anesthesiologists who practiced during the era when chloroform was in use as an anesthetic agent exhibited a low death rate for malignant neoplasms in general and for any specific category of neoplasm in particular. Their death rate for respiratory malignancies was particularly low.

The evidence from this study does not suggest that chloroform is carcinogenic in man. Since it is impossible to quantitate chloroform exposures retrospectively, neither can data from this investigation definitely refute human carcinogenicity of this agent.

*The word anesthesiologist came into use in the 1940's to describe physicians (M.D.) who gave anesthesia to distinguish them from nonmedical anesthetists such as nurses. It is used here to describe all physician-anesthetists regardless of their period of practice.

MATERIALS AND METHODS

White male anesthesiologists listed in the Directories of Anesthetists of the International Anesthesia Research Society were chosen as the population to be studied (2-6). The population was limited to white males by eliminating those with a given name of the female gender, those who were listed as female or nonwhite in the American Medical Association death file or on the death certificate. Chloroform usage was assessed by a review of the literature subsequent to 1870. Additional information was gathered from discussion with manufacturers of anesthetic agents who were in business in the early 20th century.

The total population of male anesthesiologists was obtained by counting names that appeared in the Directories for 1930, 1935, 1938, 1941, and 1948. The age distribution of the population for these years was obtained by selecting, at random. a five percent sample of names from each of these directories. The year of birth for each individual was obtained from an American Medical Directory (7-10). Ages were calculated and the percentage falling within each ten-year age group, starting at age 25, was determined. Numbers of anesthesiologists in each age group were calculated for each calendar year. The population and age distribution for intermediate years were obtained by linear interpolation. The names of male anesthesiologists appearing in the Directories for the years 1930, 1935, 1938, and 1941 were searched in the death files of the American Medical Association.

The names of all individuals found to have died between January 1, 1930 and December 31, 1946 were recorded on cards along with the date and place of death, date of birth, age, cause of death and last known address, when these were available. Copies of death certificates were requested from the registrars of vital statistics of the various states and the City of New York to verify or ascertain the cause of death. These data make up the observed causes of death of male anesthesiologists, 1930-1946.

The death rates for selected diseases occurring in this population of male anesthesiologists were compared to several other populations to examine the differences in the causes of death. Two forms of comparison of death rates were used, the proportional mortality rate, that is, the percentage of the total deaths attributable to a given cause, and the observed-to-expected mortality ratio. The populations chosen for comparison were U.S. white males, 1930-1946 (11,12), U.S. white male physicians, 1938-1942 (13,14), Metropolitan Life Insurance Company standard ordinary life insurance policyholders 1966 and members of the American Society of Anesthesiologists 1947-1956, 1957-1966, and 1967-1972 (15,16 and unpublished data of Bruce *et. al.*). Proportional mortality rate comparisons were made with anesthesiologists in later periods (1947-1972) as well as medical doctors in 1935-1942.

Expected death rates for U.S. white males 1930-1946 were determined from U.S. vital statistics rates (11) by averaging death rates for the years 1930, 1933, 1937, 1940, 1943, 1946 and for each ten-year age group between 25 and 84. Expected death rates for digestive and respiratory tract neoplasms and leukemia and aleukemia were only available for 1940 (12). These expected death rates were adjusted to the age distribution of the anesthesiologist population. For each ten-year age group, the number of anesthesiologists exposed to the risk of death was multiplied by the expected U.S. white male death rate to give the expected deaths of anesthesiologists. These expected deaths were summed for ages 25-84 and compared with the observed number of deaths. Expected death rates for male physicians (13,14) and for standard policyholders of the Metropolitan Life Insurance Company were also age adjusted to the 1930-1946 anesthesiologist population. These policyholder death rates were those used by Bruce et. al. in their studies of causes of death of anesthesiologists (15,16). Observed-to-expected mortality ratios for anesthesiologists as compared to contemporaneous white males for 1947-1956 and 1957-1966 were obtained from unpublished data of Bruce, et. al. Causes of death were classified according to 5th revision of the International List of Causes of Death *(17) for comparison with contemporaneous vital statistics rates and according to the 7th revision (18) for comparison with rates for life insurance policyholders and the data of Bruce et. al. (15,16). Deaths coded according to the fifth and earlier revisions of the International List of Causes of Death did not include Hodgkin's disease or leukemia as malignant neoplasms and available vital statistics rates do not include these diseases with malignancies.

In order to assess the validity of the mortality ratios, 95% confidence limits were computed for the major causes of death (19).

This investigation was reviewed and approved by the Institutional Review Board of Northwestern University.

*See Appendix

RESULTS AND DISCUSSION

RESULTS

Anesthesiologist Population and Deaths

The names of 274 white male anesthesiologists, who were listed in the Directories of Anesthetists of the International Anesthesia Research Society, and who died between January 1, 1930 and December 31, 1946, were located. Copies of death certificates were obtained for 261 of these deaths. In 11 instances death records were not located by vital statistics offices and one state would not release the 2 records requested without permission of next of kin. Two certificates listed only "Natural Causes" and no further information was available. Overall, 259 causes of death were obtained from copies of death certificates, 10 from the American Medical Association files and 5 remain unknown.

The size and age distribution of the population of anesthesiologists who were the subject of this study are shown in Table 1.

TABLE 1. WHITE MALE ANESTHESIOLOGIST POPULATION AND AGE DISTRIBUTION

Year		1930	1935	1938	1941	1948
Population		1119	1099	1418	1634	1972
Age Distribution		% in Age Range				
Ages	25-34	10.4	11.5	11.8	16.5	9.4
	35-44	32.3	34.4	32.9	28.2	33.0
	45-54	31.8	29.5	28.9	21.2	31.1
	55-64	20.9	21.3	15.8	22.4	21.7
	65-74	4.5	3.3	10.5	10.6	3.8
	75---	0.0	0.0	0.0	1.2	0.9

The deaths occurring among these anesthesiologists over the period 1930-1946 are given by cause and age at death (Table 2). Each death from a malignant neoplasm is listed by diagnosis and age at death in Table 3. In Table 4, the proportional mortality rates of this group of anesthesiologists are compared to U.S. physicians 1938-1942 (13,14). In Table 5, the age-adjusted ratios of deaths observed in the study population to those expected among

TABLE 2. DEATHS OF ANESTHESIOLOGISTS 1930-1946
BY AGE AND CAUSE, WHITE MALES

Cause of Death* Age	25-34	35-44	45-54	55-64	65-74	75-up	Total
ALL CAUSES	9	36	52	93	64	30	274
CARDIOVASCULAR RENAL	1	10	29	62	51	20	173
Vascular lesions of the central nervous system	0	2	7	10	13	3	35
Diseases of the heart	1	7	19	47	34	11	119
Chronic & unspecified nephritis	0	0	2	4	1	3	10
MALIGNANT NEOPLASMS	4	1	4	11	8	3	31
Digestive	2	1	1	8	5	1	18
Respiratory	0	0	0	1	0	0	1
Leukemia and aleukemia	1	0	0	0	0	0	1
Lymphosarcoma	0	0	3	0	0	0	3
ACCIDENTS	0	2	4	2	0	2	10
SUICIDES	0	2	4	4	0	0	10
ALL OTHER CAUSES	4	11	11	14	5	5	50
Infection, infectious diseases	4	6	5	2	2	1	20
Causes unknown	0	0	2	1	1	1	5

*See appendix

TABLE 3. DEATHS FROM MALIGNANT NEOPLASMS
WHITE MALE ANESTHESIOLOGISTS, 1930-1946

Cause	Age at Death
Carcinoma, tongue	63
Carcinoma, esophagus	69 74
Carcinoma, stomach	43 60 62 80
Carcinoma, colon	56 58
Carcinoma, rectum, rectosigmoid	33 33 53 66
Carcinoma, liver	63
Carcinoma, ampulla of Vater	55
Carcinoma, gall bladder	64
Carcinoma, pancreas	59 69
Carcinomatosis, abdominal viscera	62
Carcinoma, lung	57
Carcinoma, prostate	71 78 81
Carcinoma, kidney	62
Carcinoma, bladder	73
Seminoma, testicle	33
Melanotic sarcoma, eye	70
Lymphosarcoma retroperitoneal	53 53
Lymphosarcoma, spleen	54
Aleukemia	30

TABLE 4. PROPORTIONAL MORTALITY RATES OF ANESTHESIOLOGISTS AND OTHER PHYSICIANS

	DA 1930-1946*	MD 1938-1942**
	Percent	Percent
CARDIOVASCULAR-RENAL	63.1	60.0
Vascular lesion of the central nervous system	12.8	10.8
Diseases of the heart	43.4	40.7
Chronic and unspecified nephritis	3.6	5.9
MALIGNANT NEOPLASMS	11.3	10.3
Digestive	6.6	4.3
Respiratory	0.4	1.0
Leukemia, aleukemia	0.4	0.6
Lymphoid, recticuloendothelial system	1.1	---***
ACCIDENTS	3.6	4.6
SUICIDES	3.6	1.9
ALL OTHER CAUSES	18.2	23.9
Infection, infectious diseases	7.3	---***
Causes unknown	1.8	1.2

* Director of Anesthetists listings, 1930-1946 (this study).
** U.S. white male physicians, 1938-1942 (13,14).
*** A dash indicates data not available.

contemporaneous U.S. white males are shown. Ninety-five percent confidence limits are given for the major causes of death. For comparison, similar mortality ratios are shown for anesthesiologists in the subsequent two decades (Bruce, et. al., unpublished data) and for U.S. physicians, 1938-1942 (13,14).

Mortality ratios were also derived by comparing the subjects of this study to a single population, male standard ordinary policyholders of the Metropolitan Life Insurance Company (Table 6).

The leading causes of death among anesthesiologists 1930-1946 were the cardiovascular-renal diseases and malignant neoplasms. The same was true for all physicians of the same era. The comparatively high rates for suicides and the low rates for respiratory malignancies are notable. Infection and infectious diseases claimed a high proportion of lives as well.

The death rate for anesthesiologists in this study is lower than that for U.S. white males for most causes. Overall mortality from malignant neoplasms, as well as those of individual systems, is lower than that among the white male population, especially for respiratory malignancies.

The death rate for all causes in the study population is similar to that for life insurance policyholders, however, rates for certain causes do differ. Death rates from suicides and vascular lesions of the central nervous system are more than twice that of the policyholders. Cancer death rates are low, with the exception of those of the digestive organs. Respiratory cancer ratios are especially low.

Chloroform Usage

Quantitative information about the relative use of chloroform and ether as inhalation anesthetic agents is not readily available since the literature of the late 19th and early 20th centuries was generally descriptive.

Chloroform was first used clinically in 1847. Statistics given by Sykes suggest that chloroform was used for about two-thirds of all anesthetics in England in 1890, about one-half in 1920 and was rarely used by 1950 (20). In the United States, chloroform usage varied from region to region, but was apparently similar to England until the latter part of the 19th century, when its use decreased more rapidly. An article by Andrews (21) on the dangers of the two agents does contain information on the use of ether and chloroform in the 1860's (Table 7). An editorial in 1880 (22) indicated that there was a great deal of regional variation in the popularity of chloroform as an anesthetic agent in the United States and stated that "chloroform is pleasant, rapid and sure, but dangerous, therefore we hesitate and many discard it. Ether is slow, unpleasant, although vastly less dangerous, therefore, many prefer chloroform.

TABLE 5. MORTALITY RATIOS ANESTHESIOLOGISTS AND PHYSICIANS TO U.S. WHITE MALES*

	ANESTHESIOLOGISTS		M.D.'s	
	1930-1946**	1947-1956+	1957-1966+	1938-1942†
CAUSE OF DEATH				
ALL CAUSES	0.76 ± 0.92	0.74	0.51	1.02
CARDIOVASCULAR-RENAL	1.01 ± .201	1.07	0.54	1.12
Vascular lesions of the central nervous system	1.25	0.75	0.65	1.20
Diseases of the heart	1.06 ± .194	1.39	0.60	1.18
Chronic and unspecified nephritis	0.40	1.03	2.16	-- ++
MALIGNANT NEOPLASMS	0.69	0.59	0.54	0.84
Digestive	0.74††	-- ++	0.68	-- ++
Respiratory	0.18††	-- ++	0.32	-- ++
Leukemia and aleukemia	0.67††	1.18	0.83	1.75
ACCIDENTS	0.34	0.22	0.49	0.71
SUICIDES	1.03	1.22	1.44	1.04
ALL OTHER	0.46	0.34	0.22	-- ++

* Age-adjusted ratios of observed deaths among anesthesiologists and other physicians to number expected among contemporaneous U.S. white males, ± 95% confidence limits where appropriate.
** This study.
\+ Bruce, D.L., et. al., unpublished data.
† U.S. male physicians, data from Dublin and Spiegelman (13,14).
++ A dash indicates data not available.
†† Ratios to U.S. white male rates for 1940 (12).

TABLE 6. MORTALITY RATIOS
ANESTHESIOLOGISTS TO LIFE INSURANCE POLICYHOLDERS*

CAUSE OF DEATH	1930-1946**	1947-1956***	1957-1966***	1967-1972***
ALL CAUSES	1.09 ± 0.132	1.04	0.60	0.75
CARDIOVASCULAR-RENAL	1.22 ± 0.186	1.44	0.61	0.81
Vascular lesions of the central nervous system	2.16	1.30	0.77	0.89
Diseases of the heart	1.12 ± .205	1.48	0.62	0.85
MALIGNANT NEOPLASMS	0.59	0.60	0.56	0.64
Digestive	1.13	0.62	0.64	0.71
Respiratory	0.06	0.11	0.30	0.48
Leukemia and aleukemia	0.45	1.33	0.91	0.40
ACCIDENTS	0.89	0.41	0.76	0.80
SUICIDES	2.78	2.20	2.86	2.98
ALL OTHER CAUSES	1.20	0.58	0.30	0.36

* Age-adjusted ratio of observed deaths among anesthesiologists to number expected among male standard ordinary policyholders of Metropolitan Life Insurance Company, 1966, ± 95% confidence where appropriate.
** This study.
*** American Society of Anesthesiologists Members (16).

TABLE 7. COMPARISON OF ETHER AND CHLOROFORM IN THE LATE 1860's (21)

Source	Chloroform	Ether
Chicago (Hospital and Private Records	6,726	895
Bellevue Hospital, NY (1867-1869)	600	600
U.S. Army Records	13,956	6,978

In a survey by Lumbard (23) in 1906 with 79 respondents from 23 states, 67 anesthesiologists preferred ether, 7 chloroform, and 5 were noncommittal. The use of chloroform for major surgical procedures continued to decrease in the United States after the turn of the century. Its use in short procedures and particularly in obstetrics remained relatively frequent in the United States even beyond 1940 (24). A report published by the Polk County (Iowa) Medical Society Anesthetic Committee (25) reviewed the use of general and local anesthesia for major surgical procedures performed at three hospitals for the year 1923. Chloroform was used in 0.25 to 1.0 percent, ether in 62 to 90 percent and nitrous oxide in 7 to 33 percent of all anesthetics administered. Records of the Iowa Lutheran General Hospital for the years 1921, 1922 and the first six months of 1923 showed that chloroform was used in 1 percent of all anesthetics for surgery.

Chloroform continued to be used to some extent by anesthesiologists through the 1920's and 1930's and was the focus of new study by Waters and associates in the 1940's (26). Anesthetic grade chloroform was available as late as 1959 (personal communication, N. Semenuk, E.R. Squibb & Sons).

DISCUSSION

Sources of Information

Three sets of records form the basis of this investigation. They are as follows: The Directories of Anesthetists of the International Anesthesia Research Society, the death files of the American Medical Association and vital statistics records of the states and New York City. Additionally, the records of the American Society of Anesthesiologists and predecessor societies were examined. These latter records, while providing some information on deaths, are too incomplete during the era of interest to be important to this study.

The Directories of Anesthetists were not membership lists of the Society, but rather sought to list all anesthesiologists, regardless of affiliation. Each directory solicited from its readers names of physicians practicing anesthesia who were not listed. These directories are the most complete lists of anesthesiologists available for the period and are thus a sound basis for selection of a study population.

The American Medical Association published the American Medical Directory which is, "a Register of Legally Qualified Physicians of the United States." The Directory was published at 2 or 3 years intervals from 1906 through 1942 and then again in 1950. To prepare this directory, the association maintained a file with a card for each physician in the United States. Medical school graduation lists, information from state boards of registration in medicine, medical societies, etc. were the sources used to prepare this file. Physicians were requested, by mail, on a regular basis to provide information to update their listings. The file cards usually contained the physician's name, date of birth, sex, race if other than white, name of medical school, date of graduation, current and previous addresses and other information such as state and date of licensure, specialty preference, etc. When notification was received of the death of a physician, his (her) card was removed from the active file to a dead file. When removed from the active file, the date, place and often cause of death as well as the source of this information were added to the card. The obituary from the Journal of the American Medical Association was often pasted to the card. Notifications of death were received from state boards, registrars of vital statistics, medical societies, colleagues and families of the deceased. These records of the American Medical Association are the most complete records available on physicians of the period. Short of searching the vital statistics records of each state and New York City, for the seventeen-year period, they provide the best source of information available for this investigation.

Copies of death certificates were obtained by mail request from vital statistics offices. In general, cooperation of vital statistics offices was excellent, although some were slow to respond.

Mortality

Deaths occurring among anesthesiologists were examined by the proportional mortality rate, by the mortality ratios to contemporaneous U.S. white males, and to life insurance policyholders (1966). These latter comparisons were made because the desired vital statistics rates were available in appropriate details (i.e., by age, race, sex, and cause) and to allow further comparison with other physicians and with anesthesiologists in later time periods.

The proportional mortality rate is a useful tool to examine the relative importance of different diseases in causing death. The proportional rate for a given cause, however, is affected not only by changes in the number of deaths from that cause, but also by changes in numbers of deaths from other causes.

Two comparison populations were selected for calculation of age-adjusted observed-to-expected mortality ratios, U.S. white males, 1930-1946, and male life insurance policyholders (1966). Contemporary white males were exposed to the same general environment (physical, chemical, social, economic, etc.) that the anesthesiologists were. Anesthesiologists, however, being of a higher socioeconomic class probably had better nutrition, health care, and living conditions than the average white male. This, in turn, may have contributed to lower death rates. Vital statistics for different socioeconomic classes for that time period are not available. Life insurance policyholders were generally employed and of somewhat higher socioeconomic class but were not contemporaneous.

The three leading causes of death among anesthesiologists, diseases of the heart, vascular lesions of the central nervous system, and cancer were the same as those for all physicians living at the same time (13,14). Anesthesiologists had nearly double the proportion of suicides, however, data for physicians do include those for anesthesiologists; however, this should introduce little bias since less than 1% of all U.S. physicians were anesthesiologists during the study period (2-6,10).

When compared to the contemporaneous white male population, anesthesiologists have only three-fourths the expected death rate, although their rate for cardiovascular-renal diseases are about the same. The rates are lower for cancer, accidental death, and the residual (all other) causes. The lower cancer rates may have been due to earlier detection and treatment. The residual category includes the causes that were more prevalent in lower socioeconomic classes (e.g. tuberculosis). In contrast to anesthesiologists, physicians had death rates similar to white male population (13,14). Their cardiovascular-renal mortality ratios were similar to anesthesiologists. The cause for this difference in mortality from all causes combined is not clear from the available data, although cancer and accidental death ratios are lower for anesthesiologists.

When compared by mortality ratios to white males or policyholders, anesthesiologists in this study had similar death rates from all causes as did anesthesiologists 1947-1956, but were greater than those for 1957-1966 and

1967-1972. This pattern prevails for the cardiovascular-renal diseases combined, although vascular lesions of the central nervous system are a more prominent cause, and diseases of the heart less so in the study group than in the next decade.

Overall cancer death ratios changed little for anesthesiologists over the years, although digestive neoplasms were greatest during the study period. The respiratory tract neoplasm ratio increased steadily from 1930-1946 through 1967-1972, although it never reached one-half of the expected rate.

Digestive neoplasm mortality ratios for anesthesiologists did decrease after 1930-1946, especially when compared to expected rates for policyholders. It is difficult to ascribe significance to this since small numbers of deaths are involved and also because the mortality ratio to contemporaneous white males is low. The two types of malignant tumors observed in rodents fed chloroform, kidney epithelial tumors in male rats and hepatocellular carcinoma in mice of both sexes, were not a prominent cause of death of anesthesiologists (1). In the study group of anesthesiologists there was one death from cancer (carcinoma) in each of these organs, giving a proportional mortality rate of 0.004% for each. Unfortunately, comparison vital statistics are not available to calculate mortality ratios. Respiratory tract neoplasm deaths are, in contrast, remarkably low during 1930-1946 and remain low, although they do increase, until 1967-1972. The low rate observed by Bruce, et. al. in the 1947-1966 study (15) led them to investigate the cigarette smoking habits of anesthesiologists. They found no difference between anesthesiologists and the general population in their 1967-1972 study (27). Since the hazards of cigarette smoking were less well recognized prior to 1946, and since cigarettes were freely advertised in medical journals, it is unlikely that anesthesiologists smoked less than their white male contemporaries.

A possible, but speculative, explanation of the low incidence of respiratory cancer lies in the phenomenon of enzyme induction. Enzymes which metabolize xenobiotics (chemicals foreign to the biologic system) are present in the lung, liver, and other body tissues. Certain xenobiotics have the ability to induce the formation of larger quantities of enzyme, which in turn can metabolize (and often detoxify) the xenobiotic at a more rapid rate. Many inhalation anesthetics, including chloroform do induce xenobiotic-metabolizing enzymes in the liver (28) although their ability to do so in the lung has not been studied. Other xenobiotics have been shown to induce enzymes in the lung and some lung enzyme systems do metabolize carcinogens (29). Thus, it is possible that long-term exposure to chloroform or other anesthetics may speed the detoxification of inhaled carcinogens.

It was not possible to calculate mortality ratios to U.S. white males for lymphosarcoma since this cause of death was not considered separately in vital statistics rates before 1948. Data are not available for this cause of death among the life insurance policyholders.

Suicide

In their studies, Bruce, et. al. found a high incidence of suicide among anesthesiologists as compared to white males or policyholders. The rate was also high in comparison with other physicians (except opthalmologists and psychiatrists) (16). This does not appear to be true for anesthesiologists 1930-1946. Although their suicide rate was high when compared to white males or policyholders in later years, it was nearly equal to contemporaneous white males and physicians. During the depression years (1930-1940) the white male death rate for suicide was high (11).

REFERENCES

1. Report on Carcinogenesis Bioassay of Chloroform. Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institutes of Health, Bethesda, MD, March 1, 1976, 60 pp.

2. Directory of Anesthetists 1930. International Anesthesia Research Society, Avon Lake, Ohio, 1930.

3. Directory of Anesthetists 1935. International Anesthesia Research Society, Rocky River, Ohio, 1935.

4. Directory of Anesthetists 1938. International Anesthesia Research Society, Rocky River, Ohio, 1938.

5. International Directory of Anesthetists 1941. International Anesthesia Research Society, Rocky River, Ohio, 1941.

6. International Directory of Anesthetists 1948. International Anesthesia Research Society, Rocky River, Ohio, 1948.

7. American Medical Directory, 12th edition, American Medical Association, Chicago, Illinois, 1931.

8. ibid.: 14th edition, 1936.

9. ibid.: 17th edition, 1942.

10. ibid.: 18th edition, 1950.

11. U.S. Department of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics: Death Rates by Age, Race, and Sex. Vital Statistics-Special Reports 43:1956.

    1. All Causes

    11. Malignant Neoplasms, Including Neoplasms of Lymphatic and Hematopoietic Tissues.

    13. Major Cardiovascular-renal Diseases

    14. Diseases of Cardiovascular System

    15. Vascular Lesions Affecting Central Nervous System

    17. Diseases of the Heart

20. Chronic and Unspecified Nephritis and Other Renal Sclerosis.

28. Motor Vehicle Accidents

29. Accidents, Except Motor Vehicle

30. Suicides

12. Grove, R.D. and Hetzel, A.M. Vital Statistics Rates in the United States, 1940-1960. U.S. Department of Health, Education and Welfare, Public Health Service, National Center for Health Statistics, Washington, D.C. 1968.

13. Dublin, L.I. and Spiegelman, M. The Longevity and Mortality of American Physicians. JAMA, 134:1211-1215, 1947.

14. Dublin, L.I., Spiegelman, M. and Leland, R.G. Longevity and Mortality of Physicians. Postgraduate Medicine, 2:188-202, 1947.

15. Bruce, D.L., Eide, K.A., Linde, H.W. and Eckenhoff, J.E. Causes of Death Among Anesthesiologists: A 20-year Survey. Anesthesiology, 29: 565-569, 1968.

16. Bruce, D.L., Eide, K.A., Smith, N.J., Seltzer, F. and Dykes, M.H.M. A Prospective of Survey of Anesthesiologists Mortality. Anesthesiology, 41:71-74, 1974.

17. Manual of the International List of Causes of Death, based on the Fifth Decennial Revision by the International Commission, Paris, October 1938, United States Government Printing Office, Washington, D.C. 1940.

18. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 7th revision, World Health Organization, Geneva, 1957.

19. Gershenson, H. Measurement of Mortality, Society of Actuaries, Chicago, Illinois, 1961, pp. 174-177.

20. Sykes, W.S. Essays on the First Hundred Years of Anesthesia, Vol. II, E and S Livingston, Ltd., Edinburgh, 1961.

21. Andrews, E. The Relative Dangers of Anesthesia By Chloroform and Ether-Statistics of 209,893 Cases. Chicago Medical Examiner, 11:257-266, 1870.

22. Anesthetics (Editorial). Toledo Medical and Surgical Journal, 4:413-419, 1880.

23. Lumbard, J.D. Chloroform vs. Ether, Medical Record, December 1, 1906 cited in Murphy, J.B. ed., Practical Medicine Series, Vol. II General Surgery, Year Book Publishers, Chicago, Illinois, 1907. pp. 13-14.

24. Lundy, J.S. Clinical Anesthesia, W.B. Saunders Co., Philadelphia, PA 1942, pp. 414-415.

25. Report of the Anesthesia Committee, Polk County Medical Society, American Journal of Surgery, 38:59-60, 1923.

26. Waters, R.M. ed. Chloroform: A Study After 100 Years, University of Wisconsin Press, Madison, WS, 1951.

27. Bruce, D.L., Eide, K.A., Smith, N.J., Seltzer, F. and Dykes, M.H.M. Characteristics of the American Society of Anesthesiologists' Membership, 1967-1971. Anesthesiology, 41:67-70, 1974.

28. Linde, H.W. and Berman, M.L. Nonspecific Stimulation of Drug Metabolizing Enzymes by Inhalation Anesthetics. Anesthesia and Analgesia, 50: 656-667, 1971.

29. Anderson, M.W., Philpot, R.M. and Bend, J.R., et. al. Pulmonary Uptake and Metabolism of Chemicals by the Lung. In: Duncan, W.A., Leonard, B.J. eds., Clinical Toxicology, Excerpta Medica, Amsterdam, 1977, pp. 85-105.

APPENDIX

SELECTED CATEGORIES FROM INTERNATIONAL LIST OF CAUSES OF DEATH, 5th REVISION*

Causes of Death	Code Numbers
CARDIOVASCULAR AND RENAL DISEASES	58,83,90-103,131-132
Diseases of the heart	90-95
Chronic and unspecified nephritis	131-132
Acute rheumatic fever	58
Vascular lesions of the central nervous system	83
Pericarditis	90
Acute endocarditis	91
Chronic affections of the valves and endocardium	92
Diseases of the myocardium	93
Diseases of the coronary arteries and angina pectoris	94
Other diseases of the heart	95
Aneurysm	96
Arteriosclerosis	97
Gangrene	98
Other diseases of the arteries	99
Diseases of the veins	100
Diseases of the lymphatic system	101
High blood pressure	102
Other diseases of the circulatory system	103
MALIGNANT NEOPLASMS	44b,45-55,74
Lymphogranulomatosis (Hodgkin's disease)	44b
Cancer of the buccal cavity and pharynx	45
Cancer of the digestive organs and peritoneum	46
Cancer of the respiratory system	47
Cancer of the uterus+	48
Cancer of other female genital organs+	49
Cancer of the breast	50
Cancer of the male genital organs	51
Cancer of the urinary organs	52
Cancer of the skin	53
Cancer of the brain and other parts of the central nervous system	54
Cancer of other and unspecified organs	55
Leukemias and aleukamias	74

*Reference (17)

+None observed in this study of males only

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA-600/1-79-043		

4. TITLE AND SUBTITLE	5. REPORT DATE
Causes of Death of Anesthesiologists from the Chloroform Era	October 1979 issuing date
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
Harry W. Linde and Paul S. Mesnick	
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
Northwestern University Chicago, Illinois 60611	11. CONTRACT/GRANT NO. Grant No. R805473
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Health Effects Research Laboratory- Cinn, OH Office of Research & Development U.S. Environmental Protection Agency Cincinnati, Ohio 45268	Final - 1-1-30 - 12-31-46 14. SPONSORING AGENCY CODE EPA/600/10

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This investigation was undertaken to determine if there were an excess of cancer deaths occurring in anesthesiologists who practiced in an era when chloroform was in use and to estimate the degree of chloroform usage during that era. Causes of death of anesthesiologists dying between 1930 and 1946 were determined.

Death rates in this group of anesthesiologists were compared to rates for U.S. white males, male physicians, anesthesiologists in later decades, and life insurance policyholders. Combined death rates were lower among anesthesiologists than the U.S. male population but exceeded them for some cardiovascular diseases. Death rates for combined malignant neoplasms were low, with digestive organ neoplasms being the most common. Death rates from malignancies of the respiratory tract were unusually low.

Anesthesiologists in the United States in the late 19th and early 20th centuries appear to have been occupationally-exposed to chloroform vapor. Their death rates from all malignant neoplasms and from those of the digestive organs are somewhat greater than for anesthesiologists several decades later. No firm conclusions on carcinogenesis can be drawn, however, because of the small population and small number of deaths involved and the different age distributions of the groups of anesthesiologists.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Chloroform, epidemiology, malignant neoplasms, heart diseases, anesthesiology, physicians, mortality		06/J

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Release to Public	Unclassified	30
	20. SECURITY CLASS *(This page)*	22. PRICE
	Unclassified	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE ☆ U.S. GOVERNMENT PRINTING OFFICE: 1979-657-146/5486