CENTER FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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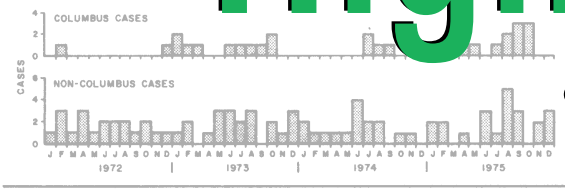
Epidemiologic Notes and Reports

Acute Childhood Leukemia — Columbus, Ohio

From August-October 1975, 8 cases of acute leukemia were diagnosed at Columbus Children's Hospital [illegible] Columbus, Ohio, in children living [illegible] city. During a consecutive 3-month period in 1975 [illegible] 1974, the greatest number of cases of acute leukemia diagnosed at the hospital in Columbus children was [illegible] (Figure 1).

FIGURE 1. Acute Leukemia [illegible] Children's Hospital, 1972-1975 — by Place of Residence and Date of Diagnosis



To evaluate this cluster of illness, all cases of acute leukemia diagnosed at Columbus Children's Hospital in 1972-1975 were reviewed with respect to age, race, sex, type of leukemia, date of diagnosis, and residence in and outside of Columbus (Table 1). [illegible] hospital records [illegible] children with leukemia in Columbus [illegible] patients from surrounding areas. [illegible] 1974, an average of 5.3 cases of [illegible] were seen each year among Columbus residents (the expected number is 6.1, based on age-specific rates from the Third National Cancer Survey [*1*]). Over the 4-year period 1972-1975, 107 cases were seen, 28 among Columbus residents. Both Columbus and non-Columbus patients in 1975 were somewhat older and included relatively more females than in earlier years. Case distributions by race and leukemic cell type were not unusual.

Twelve cases were diagnosed in Columbus residents in 1975, compared with a total of 16 for all 3 preceeding years. To assess the possibility of time-space clustering among Columbus cases over the entire 4-year period a statistical analysis was performed using the procedure devised by Knox (*2*). No statistically significant clustering was found; 13 case-pairs were observed in which dates of diagnosis were less than 1 year apart and places of residence 1 mile or less apart, whereas 14.4 pairs were to be expected on a random basis. Inspection of the 1975 case data showed no topographic clustering and no obvious community or family interrelationships among cases. No evidence of seasonal periodicity was [illegible] testing by month of diagnosis for [illegible] years.

Reported by [illegible], Columbus Children's Hospital, Columbus, Ohio; [illegible], MD, MPH, State Epidemiologist, Ohio Department of Health; [illegible], Cancer and Birth Defects Div, Bur of Epidemiology, CDC.

Editorial Note: The question of time-space clustering among cases of leukemia and lymphoma has received considerable epidemiologic attention, particularly in connection with hypotheses regarding the possible viral etiology of cancer. While no evidence has been found of statistically significant time-space clustering among adult cases, several studies have suggested such a tendency among cases of childhood acute leukemia (*2-5*). The significance of such observations remains unclear. In the present investigation no evidence, statistical or otherwise, was found to suggest that the recent case cluster in Columbus might be due to factors other than

TABLE 1. Acute Leukemia, Columbus Children's Hospital, 1972-1975 — by Place of Residence, and Year of Diagnosis

		Year of Diagnosis			
		1972-1974		1975	
		Columbus Residents	Other	Columbus Residents	Other
Total number of cases		16	57	12	22
Mean age at diagnosis		4.5	5.4	7.0	6.5
Sex:	Male	10	33	5	11
	Female	6	19	7	11
Race:	White	13	55	9	21
	Black	3	2	0	1
	Other	0	0	1	0
	Unknown	0	0	2	0
Leukemic Cell Type:					
	Myelocytic	3	11	3	4
	Monocytic	2	2	0	0
	Lymphocytic or Stem Cell	11	44	9	18

Highlights in Public Health

Landmark Articles from the *MMWR* 1961–1996

Morbidity and Mortality Weekly Report

PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Prepared by the COMMUNICABLE DISEASE CENTER MElrose 4-5131

For release January 13, 1961 Atlanta 22, Georgia Vol. 10, No. 1

Provisional Information on Selected Notifiable Diseases in the United States and on Deaths in Selected Cities for Week Ended January 7, 1961

With the production of this issue of the Morbidity and Mortality weekly Report, the Communicable Disease Center has assumed responsibility for the collection and publication of data on notifiable diseases reported by the States and Puerto Rico and deaths reported by 123 major cities.

The Center welcomes the addition of this important function. We believe the closer current contact with those reporting morbidity and mortality data will better permit us more rapidly and successfully to carry out our primary role of providing consultation and assistance to the States when communicable disease problems occur.

The collection of morbidity data by the Public Health Service had its beginning more than 80 years ago when Congress authorized the compilation and publication of data on cholera, smallpox, plague and yellow fever. Prior to 1900, however, monthly and annual summaries of notifiable diseases were received from only a few States and cities. The number of States reporting gradually increased and in 1912, the Tenth Annual Conference of State and Territorial Health Authorities recommended weekly telegraphic reporting for selected communicable diseases. Until 1949, the weekly morbidity and mortality statistics were published in Public Health Reports. In 1949 this

Table I. Cases of Specified Notifiable Diseases: United States

(Cumulative totals include revised and delayed reports through previous week)

Disease (Seventh Revision of International Lists, 1955)	1st Week			Cumulative						Approximate seasonal low point
				First week			Since seasonal low week			
* Weekly incidence low or sporadic --- Data not available - Quantity zero	Ended Jan. 7, 1961	Ended Jan. 9, 1960	Median 1956-60	1961	1960	Median 1956-60	1960-61	1959-60	Median 1955-56 to 1959-60	
Anthrax----------082	-	-	*	-	-	*	*	*	*	*
Botulism----------049.1	-	3	*	-	3	*	*	*	*	*
Brucellosis (undulant fever)------044	9	10	10	9	10	10	*	*	*	*
Diphtheria----------055	20	31	24	20	31	24	600	569	779	July 1
Encephalitis, infectious----------082	25	23	20	25	23	20	25	23	20	Jan. 1
Hepatitis, infectious, and serum----------092,N998.5 pt.	1,014	594	385	1,014	594	385	16,189	8,614	5,475	Sept. 1
Malaria----------110-117	1	1	*	1	1	*	*	*	*	*
Measles----------085	6,261	7,076	6,650	6,261	7,076	6,650	42,308	45,148	43,319	Sept. 1
Meningitis, aseptic----------340 pt.	25	30	---	25	30	---	25	30	---	Jan. 1
Meningococcal infections----------057	37	36	54	37	36	54	691	686	860	Sept. 1
Poliomyelitis----------080	14	17	29	14	17	29	3,078	8,291	8,291	Apr. 1
Paralytic----------080.0,080.1	8	12	17	8	12	17	2,117	5,513	5,513	Apr. 1
Nonparalytic----------080.2	3	1	7	3	1	7	624	2,118	2,118	Apr. 1
Unspecified----------080.3	3	4	5	3	4	5	337	660	660	Apr. 1
Psittacosis----------096.2	1	1	*	1	1	*	*	*	*	*
Rabies in man----------094	-	-	*	-	-	*	*	*	*	*
Streptococcal sore throat, including scarlet fever------050,051	7,596	6,977	---	7,596	6,977	---	105,248	---	---	Aug. 1
Typhoid fever----------040	6	6	13	6	6	13	692	732	1,023	Apr. 1
Typhus fever, endemic----------101	1	-	*	1	-	*	*	*	*	*
Rabies in animals----------	42	67	86	42	67	86	612	1,051	1,035	Oct. 1

First issue of *MMWR* published by CDC

Highlights in Public Health

Landmark Articles from the *MMWR* 1961–1996

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PREFACE

This volume is a compendium of articles from the *Morbidity and Mortality Weekly Report* (*MMWR*) that were prepared on the occasion of the 50th anniversary of CDC, marked on July 1, 1996. The compendium comprises articles from the *MMWR* weekly selected primarily on the basis of their historical merit and interest to public health practice. For each of the 20 selections, we invited past and/or current CDC experts (and, in some cases, experts from outside CDC) to write a new editorial note about some aspect of each article and its relation to the evolution of public health practice.

The topics of these reports span the scope of public health problems addressed and reported by CDC in *MMWR* after responsibility for *MMWR* came to CDC in 1961. The new editorial notes for many of these reports were contributed to by persons who played key roles in responses to the problems at the time they occurred; we encouraged these contributors to share perspectives and details of special historical interest. We hope the reprinted reports and new commentaries are serviceable not only to local and state public health officials, who contribute to and use *MMWR*, but also by public health and medical practitioners in other settings, schools of public health, and other academic programs with concentrations in the history and policies of health.

MMWR's history is intertwined with the evolution of public health in the United States. In the spring of 1878, Congress passed the first National Quarantine Act requiring U.S. consuls to report sanitary conditions abroad and on vessels bound for U.S. ports. From these and other sources, the Surgeon General of the Public Health Service (PHS) was directed to publish weekly abstracts for transmission to PHS medical officers, collectors of customs, and state and local health authorities. Thus, on July 13, 1878, under the name, *Bulletin No. 1*, the predecessor of *MMWR* was born. The *Bulletins* lasted barely 46 issues, but they chronicled such grim and terrifying events as the great yellow fever epidemic of the Mississippi Valley.

The National Board of Health and its quarantine reports followed the *Bulletin*. Publication resumed, however, in 1887 when No. 47 appeared as the *Weekly Abstract of Sanitary Reports*. Although only a few pages, it reached 1800 readers and was, according to its editor, "greatly appreciated not only by quarantine officers, but by steamship companies, merchants, and the press." By 1897, the *Abstract* became *Public Health Reports*, a weekly journal devoted to reporting epidemics and morbidity and mortality, but scientific articles as well. Several federal agencies sponsored this publication during the first half of the century, and by 1952 *MMWR* acquired its present name, published then by the National Office of Vital Statistics. However, in 1960, CDC (then the Communicable Disease Center) was given the responsibility, and the first issue published by CDC appeared on January 13, 1961.

Distributing objective scientific information, albeit often preliminary, to the public at large, *MMWR* has filled that critical time gap between the immediacy of the news media's interpretation and the long wait for publication in the scientific journals. In fact, CDC has published extra issues when health events of national importance required immediate, scientific, and objective reporting. For example, the 1970–71 nationwide epidemic of bacteremia associated with contaminated intravenous fluids and the 1976 occurrence of Guillain-Barré syndrome associated with the swine influenza vaccination program demanded immediate reporting to the nation that *MMWR* provided.

The primary purpose of *MMWR* has been to report events of public health interest and importance to CDC's major constituents—state and local health departments—and as quickly as possible. In large part, they are the ones who recognize and report the data to CDC and, therefore, they should receive the greatest credit for the *MMWR*'s role in prevention and control of morbidity and mortality.

Our experiences as Editors of the *MMWR* span 3 decades and most of the history of the *MMWR* at CDC. We are proud of the accomplishments of the *MMWR* on behalf of CDC and in the service of public health in the United States and worldwide, and we are pleased to present this compendium. We hope you find it helpful in the study and practice of public health.

Richard A. Goodman, M.D., M.P.H.
Editor, 1988–1998

Karen L. Foster, M.A.
Assistant Editor, 1982–1986;
Managing Editor, 1988–

Michael B. Gregg, M.D.
Editor, 1967–1988

In this compendium, we have corrected typographic inconsistencies and errors published both in the original reports and in the reprinted reports with new editorial notes. We have changed text references to page numbers and table and figure call-outs to reflect the pagination of this volume. Tables and figures appear inconsistent only because we attempted to recreate their original style and format.

FOREWORD

CDC. *MMWR.* Public health. Respect. Timeliness. Efficiency. Protecting the health of the public. All synonymous. All American. Now global. A source of pride and trust for us all. The Centers for Disease Control and Prevention.

In 1996, the original CDC celebrated its 50th anniversary. CDC logically began right after the Second World War at a time when the United States of America began to put a lot of money and effort into health improvements for its people. The Depression was over, as was the world's great war. Such movements as the GI Bill for education, the beginning of the baby boomers generation, and greatly increased funding for the National Institutes of Health were under way. Many new public medical schools were being founded, and federal legislation (Hill-Burton Act) enabled the construction of hundreds of needed hospitals, especially in small cities and towns and rural areas. The booming nation, in an uneasy peace after its largest war, focused inwardly to improve the lot of its people while it looked outwardly with apprehension toward world communism, especially in the USSR and Red China, and toward the extreme horror of nuclear war.

World War II literally had brought home the reality of tropical diseases to all Americans because of the stationing of troops from all 48 states in the North African and South Pacific campaigns where malaria, in particular, was such a ubiquitous scourge. And, of course, yellow jaundice (later known as hepatitis A) was also rampant in many military arenas. Some believe that Hitler lost the battle of Stalingrad not only because of the Russian winter, overextended supply lines, and tenacious Russian resistance, but because hepatitis decimated his German army there.

Beginning the CDC in Georgia was also sensible since the U.S. South was still home to endemic malaria, intestinal parasites, and many other infectious diseases (I had both malaria and hookworm, growing up in the neighboring state of Alabama in the decade of the founding of CDC). The *MMWR,* established in 1878, became a regular CDC responsibility in 1961 and now issues its first book of landmark articles. Looking through the landmark article list, all are obviously notable but some are really stickouts.

1963 and 1978—smallpox. Yes, dear younger readers, there was once such a disease, and what a terrible scourge it was. Sweden was the first country in the world to eliminate indigenous smallpox—in 1895. Yet, in 1963 there was an outbreak in Sweden from a case brought from Indonesia, telegraphing the interconnectivity of humans and infectious diseases in our global village. That experience helped stimulate Sweden to join with the United States to lead in global smallpox eradication, the last human case being reported in the *MMWR* in 1978. Modern public health really began in 1796, 200 years before the CDC's 50th anniversary, when Edward Jenner discovered immunization—cowpox preventing smallpox. And CDC, especially D.A. Henderson and William F. Foege, deserves more credit than anyone else (except for Jenner, of course) for eliminating human clinical smallpox from the world.

It has been wonderfully in the public interest for the CDC to have expanded from its original "Communicable Disease Center" founding name and mission to a much broader base—any and all diseases that are preventable. Preventable chemical injuries (poisonings and toxicology) have been a noteworthy focus of CDC work. And, of course, that most important chemical injury of them all—tobacco toxicity and carcino-

genicity—following chronic nicotine addiction. CDC called cigarette smoking a nationally notifiable condition in CDC's 50th year—1996—another landmark.

For the future, there is plenty still on CDC's plate. Death is normal. But premature deaths from any and all causes, many of them behavioral, are not normal—like drug addiction (including alcohol, tobacco and illicit drugs); like violence—injuries, intentional or unintentional (CDC early on pointed out that there is no such thing as an "accident," only unintentional injury); like cancers of a wide variety of types that are known to be preventable; like undesired, unexpected pregnancy and its frequently harmful consequences. All are significant; all are controversial; all are CDC's.

In contrast to the everyday practice of medicine, which is very personal and one-on-one, public health is for population groups and often controversial by its very nature. Many public health measures, once data are in and truth is known, must be brought about by law change. We can never expect such necessary coercion to be uniformly popular, but it is required from time to time. And one can expect the politicians to raise a ruckus (including about budget) with CDC when it tackles particularly controversial issues (such as firearm injury prevention).

In a sense it is ironic that we may have come full circle with infectious diseases, especially new or changed, or unknown, or unpredictable, or even unknowable, as global microbial threats again rear their ugly heads and tempt CDC to take a swing at them. CDC will swing, and we all will be very proud and comfortable that CDC and its stellar publication *MMWR* are still around, going strong and unequivocally in the public's best interest. Of historic significance, the stellar leader of CDC during 1993–1998, David Satcher, MD, now travels from his native Alabama through Los Angeles, Nashville, and Atlanta to take on the challenge of becoming the new Surgeon General of the U.S. Public Health Service and Assistant Secretary of Health of the U.S. Department of Health and Human Services. Yet another validation of the mission, scope, and vitality of our national treasure—the Centers for Disease Control and Prevention.

George D. Lundberg, M.D.
Editor, *Journal of the American Medical Association*

HISTORY OF CDC

History of CDC

MMWR 1996;45:526–30 (June 28, 1996)

CDC, an institution synonymous around the world with public health, will be 50 years old on July 1. The Communicable Disease Center was organized in Atlanta, Georgia, on July 1, 1946; its founder, Dr. Joseph W. Mountin, was a visionary public health leader who had high hopes for this small and comparatively insignificant branch of the Public Health Service (PHS). It occupied only one floor of the Volunteer Building on Peachtree Street and had fewer than 400 employees, most of whom were engineers and entomologists. Until the previous day, they had worked for Malaria Control in War Areas, the predecessor of CDC (Figure 1), which had successfully kept the southeastern states malaria-free during World War II and, for approximately 1 year, from murine typhus fever. The new institution would expand its interests to include all communicable diseases and would be the servant of the states, providing practical help whenever called.

Distinguished scientists soon filled CDC's laboratories, and many states and foreign countries sent their public health staffs to Atlanta for training. Any tropical disease with an insect vector and all those of zoological origin came within its purview. Dr. Mountin was not satisfied with this progress, and he impatiently pushed the staff to do more. He reminded them that except for tuberculosis and venereal disease, which

FIGURE 1. Malaria Control in War Areas, Henry Rose Carter Laboratory — Savannah, Georgia, 1944

had separate units in Washington, D.C., CDC was responsible for any communicable disease. To survive, it had to become a center for epidemiology.

Medical epidemiologists were scarce, and it was not until 1949 that Dr. Alexander Langmuir arrived to head the epidemiology branch. He saw CDC as "the promised land," full of possibilities. Within months, he launched the first-ever disease surveillance program, which confirmed his suspicion that malaria, on which CDC spent the largest portion of its budget, had long since disappeared. Subsequently, disease surveillance became the cornerstone on which CDC's mission of service to the states was built and, in time, changed the practice of public health.

The outbreak of the Korean War in 1950 was the impetus for creating CDC's Epidemic Intelligence Service (EIS). The threat of biological warfare loomed, and Dr. Langmuir, the most knowledgeable person in PHS about this arcane subject, saw an opportunity to train epidemiologists who would guard against ordinary threats to public health while watching out for alien germs. The first class of EIS officers arrived in Atlanta for training in 1951 and pledged to go wherever they were called for the next 2 years. These "disease detectives" quickly gained fame for "shoe-leather epidemiology" through which they ferreted out the cause of disease outbreaks.

The survival of CDC as an institution was not at all certain in the 1950s. In 1947, Emory University gave land on Clifton Road for a headquarters, but construction did not begin for more than a decade. PHS was so intent on research and the rapid growth of the National Institutes of Health that it showed little interest in what happened in Atlanta. Congress, despite the long delay in appropriating money for new buildings, was much more receptive to CDC's pleas for support than either PHS or the Bureau of the Budget.

Two major health crises in the mid-1950s established CDC's credibility and ensured its survival. In 1955, when poliomyelitis appeared in children who had received the recently approved Salk vaccine, the national inoculation program was stopped. The cases were traced to contaminated vaccine from a laboratory in California; the problem was corrected, and the inoculation program, at least for first and second graders, was resumed. The resistance of these 6- and 7-year-olds to polio, compared with that of older children, proved the effectiveness of the vaccine. Two years later, surveillance was used again to trace the course of a massive influenza epidemic. From the data gathered in 1957 and subsequent years, the national guidelines for influenza vaccine were developed.

CDC grew by acquisition. The venereal disease program came to Atlanta in 1957 and with it the first Public Health Advisors, nonscience college graduates destined to play an important role in making CDC's disease-control programs work. The tuberculosis program moved in 1960, immunization practices and the *MMWR* in 1961. The Foreign Quarantine Service, one of the oldest and most prestigious units of PHS, came in 1967; many of its positions were soon switched to other uses as better ways of doing the work of quarantine, primarily through overseas surveillance, were developed. The long-established nutrition program also moved to CDC, as well as the National Institute for Occupational Safety and Health, and work of already established units increased. Immunization tackled measles and rubella control; epidemiology added family planning and surveillance of chronic diseases. When CDC joined the international malaria-eradication program and accepted responsibility for protecting the earth from moon germs and vice versa, CDC's mission stretched overseas and into space.

CDC played a key role in one of the greatest triumphs of public health: the eradication of smallpox. In 1962 it established a smallpox surveillance unit, and a year later tested a newly developed jet gun and vaccine in the Pacific island nation of Tonga. After refining vaccination techniques in Brazil, CDC began work in Central and West Africa in 1966. When millions of people there had been vaccinated, CDC used surveillance to speed the work along. The World Health Organization used this "eradication escalation" technique elsewhere with such success that global eradication of smallpox was achieved by 1977. The United States spent only $32 million on the project, about the cost of keeping smallpox at bay for 2½ months.

CDC also achieved notable success at home tracking new and mysterious disease outbreaks. In the mid-1970s and early 1980s, it found the cause of Legionnaires disease and toxic-shock syndrome. A fatal disease, subsequently named acquired immunodeficiency syndrome (AIDS), was first mentioned in the June 5, 1981, issue of *MMWR*. Since then, *MMWR* has published numerous follow-up articles about AIDS, and one of the largest portions of CDC's budget and staff is assigned to address this disease.

Although CDC succeeded more often than it failed, it did not escape criticism. For example, television and press reports about the Tuskegee study on long-term effects of untreated syphilis in black men created a storm of protest in 1972. This study had been initiated by PHS and other organizations in 1932 and was transferred to CDC in 1957. Although the effectiveness of penicillin as a therapy for syphilis had been established during the late 1940s, participants in this study remained untreated until the study was brought to public attention. CDC also was criticized because of the 1976 effort to vaccinate the U.S. population against swine flu, the infamous killer of 1918–19. When some vaccinees developed Guillain-Barré syndrome, the campaign was stopped immediately; the epidemic never occurred.

As the scope of CDC's activities expanded far beyond communicable diseases, its name had to be changed. In 1970 it became the Center for Disease Control, and in 1981, after extensive reorganization, Center became Centers. The words "and Prevention" were added in 1992, but, by law, the well-known three-letter acronym was retained. In health emergencies CDC means an answer to SOS calls from anywhere in the world, such as the recent one from Zaire where Ebola fever raged.

Fifty years ago CDC's agenda was noncontroversial (hardly anyone objected to the pursuit of germs), and Atlanta was a backwater. In 1996, CDC's programs are often tied to economic, political, and social issues, and Atlanta is as near Washington as the tap of a keyboard (Figure 2).

Adapted for MMWR *by Elizabeth W Etheridge, PhD, from her book,* Sentinel for Health: A History of the Centers for Disease Control. *Berkeley, California: University of California Press, 1992.*

Editorial Note: When CDC's name changed in 1970, from the Communicable Disease Center to the Center for Disease Control, CDC scientists were poised to accept new challenges. The most notable of the agency's many achievements in the following 10 years was its role in global smallpox eradication, a program that finally succeeded because of the application of scientific principles of surveillance to a complex problem. In the realm of infectious diseases, CDC maintained its preeminence, identifying the Ebola virus and the sexual transmission of hepatitis B, and isolating the hepatitis C virus and the bacterium causing Legionnaires disease. The Study of the Effectiveness of Nosocomial Infection Control (SENIC) was the most expensive study the agency had ever undertaken and proved for the first time the effectiveness of recom-

FIGURE 2. CDC headquarters on Clifton Road — Atlanta, 1996

mended infection-control practices. Other studies included identification of the association of Reye syndrome with aspirin use, the relation between liver cancer and occupational exposure to vinyl chloride, and the harmful effects of the popular liquid protein diet.

The 1980s institutionalized what is considered to be a critically important scientific activity at CDC—the collaboration of laboratorians and epidemiologists. The decade began with the national epidemic of toxic-shock syndrome, documentation of the association with a particular brand of tampons, and the subsequent withdrawal of that brand from the market. CDC collaboration with the National Center for Health Statistics (NCHS) resulted in the removal of lead from gasoline, which in turn has markedly decreased this exposure in all segments of the population. The major public health event of the 1980s was the emergence of AIDS. CDC helped lead the response to this epidemic, including characterization of the syndrome and defining risk factors for disease.

CDC became involved in two very large epidemiologic studies during the 1980s. First, the Cancer and Steroid Hormone Study conducted in collaboration with the National Cancer Institute assessed the risks for breast, cervical, and ovarian cancers associated with both oral contraceptives and estrogen replacement therapy. Second, at the request of Congress, CDC undertook a series of studies of the health effects of service in Vietnam on veterans and their offspring, which led to a landmark contribution of the laboratory—the development of a serum test for dioxin able to measure the toxicant in parts per quadrillion. This decade also introduced scientifically based rapid assessment methods to disaster assistance and sentinel health event surveillance to occupational public health. Epi Info, a software system for the practice of applied

epidemiology, was introduced and now has been translated into 12 languages for tens of thousands of users globally. Finally, during the 1980s, NCHS was moved to CDC, further enhancing CDC's information capabilities to meet national needs.

The 1990s have been characterized by continuing applications of CDC's classic field-oriented epidemiology, as well as by the development of new methodologies. For example, the disciplines of health economics and decision sciences were merged to create a new area of emphasis—prevention effectiveness—as an approach for making more rational choices for public health interventions. In 1993, the investigation of hantavirus pulmonary syndrome required a melding between field epidemiology and the need for sensitivity to and involvement of American Indians and their culture. Similarly, the response to global problems with Ebola virus and plague underscore the importance of adapting these new methodologies. Other major CDC contributions to the world's health include global polio eradication efforts and efforts to prevent neural tube defects. Finally, in October 1992, Congress changed CDC's official name to the Centers for Disease Control and Prevention, to recognize CDC's leadership role in prevention. Today, CDC is both the nation's prevention agency and a global leader in public health. As the world enters the new millennium, CDC will remain the agency ready to address the challenges to its vision of healthy people in a healthy world through prevention.

Editorial Note by: Stephen B Thacker, MD, MSc, Office of the Director, Epidemiology Program Office, CDC.

Notifiable Disease Surveillance and Notifiable Disease Statistics — United States, June 1946 and June 1996

MMWR 1996;45:530–6 (June 28, 1996)

National surveillance for infectious diseases is used to document the morbidity and impact associated with these conditions in the United States. This report includes morbidity data for the weeks ending June 8, 1946, and June 22, 1996, and describes changes since 1946 both in the procedures for conducting surveillance and in the incidence of selected diseases.

Surveillance Notes

The history of the reporting and tracking of diseases that could pose a risk to public health in the United States dates back more than a century. In 1878, Congress authorized the U.S. Marine Hospital Service (the forerunner of today's Public Health Service [PHS]) to collect morbidity reports on cholera, smallpox, plague, and yellow fever from U.S. consuls overseas; this information was used to institute quarantine measures to prevent the introduction and spread of these diseases into the United States. In 1879, a specific Congressional appropriation was made for collecting and publishing reports of these notifiable diseases. The authority for weekly reporting and publication was expanded by Congress in 1893 to include data from states and municipal authorities. By 1928, all states, the District of Columbia, Hawaii, and Puerto Rico were reporting 29 infectious diseases to the Surgeon General.

Fifty years ago, morbidity statistics published each week were accompanied by the statement "No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring." These statistics appeared under the heading "Prevalence of Disease—United States" in each issue of *Public Health Reports* printed by PHS, Office of the Surgeon General (Division of Public Health Methods) (see pages 12–15). In 1949, the collection, compilation, and publication of these morbidity statistics was transferred to the National Office of Vital Statistics, which produced the *Weekly Morbidity Report*. In 1952 the publication was renamed *Morbidity and Mortality Weekly Report*, and responsibility for the publication was transferred to CDC in 1961.

In 1946, reports of notifiable diseases consisted of summary statistics, transmitted by telegram each week by all state and some city health officers. The numbers were tabulated and sent immediately by letter to each site for verification. Data published in the June 28, 1946, issue of *Public Health Reports* were for the week ending June 8, 1946 (see pages 12–15). Today, for most diseases, each state health department enters individual case reports (rather than summary numbers) into a computer for transmission to CDC through the National Electronic Telecommunications System for Surveillance; data published in this issue of *MMWR* represent cumulative totals reported through June 22, 1996. Except for New York City and Washington, D.C., morbidity data from individual cities are no longer published weekly.

Because the reporting frequency varied for different conditions (i.e., weekly, monthly, or annually), the precise number of conditions considered nationally reportable in 1946 is unclear. The first list of 41 infectious diseases that all states agreed should be nationally notifiable to PHS was developed at the first conference of state and territorial epidemiologists in 1951 (*1*). This group was the forerunner of the Coun-

cil of State and Territorial Epidemiologists (CSTE), now CDC's primary collaborator for determining what is nationally reportable. In 1951, as now, because reporting can be mandated only at the state level, reporting to CDC by the states was voluntary. Today, 52 infectious diseases are notifiable nationally (*2*); in addition, at the 1995 CSTE meeting, the first noninfectious condition—elevated blood lead levels—was added to the list of conditions designated as reportable at a national level (*3*). On June 6, 1996, CSTE added silicosis and acute pesticide poisoning/injuries to the list of nationally reportable conditions. Also on June 6, CSTE unanimously agreed to include **prevalence of cigarette smoking** in the list of conditions designated as reportable by states to CDC; this is the first time tobacco has been included and the first time a risk behavior, rather than a disease or illness, has been included (see page 29).

Disease Notes

Comparing reports of notifiable conditions during June 1946 and June 1996 highlights some of the differences in the prevalent or common diseases. For example, 50 years ago, in the fundamentally prevaccine era, for the week ending June 8, 1946, health departments reported 161 cases of poliomyelitis, 229 cases of diphtheria, 1886 cases of pertussis, and 25,041 cases of measles (see page 13–15). Through the week ending June 22, 1996, a cumulative total of no confirmed cases of polio, one case of diphtheria, 1419 cases of pertussis, and 263 cases of measles have been reported for 1996. Since 1946, vaccines have been licensed for all four of these conditions: diphtheria and tetanus toxoids and pertussis vaccine in 1949, inactivated polio vaccine in 1955 and live attenuated vaccine in 1961, and measles vaccine in 1963. Because of the advent of these and other disease-control strategies, during the past decade public health authorities have established as targets for the year 2000 eradication of polio globally and measles elimination in the Americas. Four cases of another vaccine-preventable disease, smallpox, were reported for the week ending June 8, 1946, and a total of 337 cases for the entire year of 1946; the last documented cases of smallpox in the United States occurred 3 years later, in 1949. In 1958, the World Health Organization targeted smallpox for global eradication, a campaign that was declared successful in 1980 (*4*).

Among the 10 nationally notifiable infectious diseases that are most commonly reportable today, several were unknown in June 1946. The 10 most frequent nationally reportable infectious conditions in 1994 (the most recent year for which final data are available) were, in descending order, gonorrhea, acquired immunodeficiency syndrome (AIDS), salmonellosis, shigellosis, hepatitis A, tuberculosis, primary and secondary syphilis, Lyme disease, hepatitis B, and pertussis (*5*). Fifty years ago, AIDS and Lyme disease were unknown. "Infectious hepatitis" (subsequently identified as hepatitis A) had just been identified, and morbidity reports for this condition first appeared in 1947. In 1953, serum hepatitis (subsequently named hepatitis B) was recognized as a separate entity, although it was included in the general category of hepatitis until 1966, when infectious and serum hepatitis began to be reported separately. Other diseases reported on a weekly basis during 1946 included amebiasis, murine typhus fever, and tularemia; during the past 10 years, these three conditions were deleted from the nationally notifiable disease list and are no longer routinely reported to CDC.

Because of the acknowledged underreporting of most diseases (particularly those typically characterized by clinically mild illness) to this passive surveillance system, the National Notifiable Disease Surveillance System (NNDSS) does not capture all

cases of disease nationwide. However, these data are essential for monitoring disease trends and for determining relative disease burdens. In addition, this same NNDSS—with origins dating more than a century ago—continues to be used for monitoring the decline in incidence of vaccine-preventable and other diseases and to detect and document the appearance of new public health problems.

Reported by: Systems Operations and Information Br, Div of Surveillance and Epidemiology, Epidemiology Program Office, CDC.

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PREVALENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED JUNE 8, 1946

Summary

A total of 161 cases of poliomyelitis was reported for the week, as compared with 145 last week and 92 for the corresponding week last year. The latter figure was the largest reported for a previous corresponding week in the past 11 years. States reporting 5 or more cases are as follows (last week's figures in parentheses): *Increases*—New York 6 (4), Kansas 7 (1), Florida 33 (31), Louisiana 9 (3), Texas 35 (26), California 15 (11): *decreases*—Alabama 15 (26), Colorado 5 (6). The total to date for the country as a whole is 1,195, as compared with 903 for the same period last year. Since March 16 (the approximate date of lowest weekly incidence in both years) 729 cases have been reported, as compared with 506 for the same period last year and a 5-year median for the period of 323.

No new case of smallpox was reported during the week in either California or Washington. Only 4 cases were reported for the country as a whole—1 each in Illinois, Iowa, Kansas, and Colorado. The total to date (of which 13 occurred in California and 68 in Washington) is 236, as compared with 224 for the same period last year and a 5-year median of 514.

A further slight decrease occurred in the incidence of measles. Of the total of 25,041 cases reported currently, as compared with 26,347 last week and a 5-year median of 14,662, approximately 68 percent occurred in the New England, Middle Atlantic, and East North Central areas. The total for the year to date is 567,487, as compared with 79,259 and 551,742, respectively, for the same periods of 1945 and 1944.

A total of 229 cases of diphtheria was reported, as compared with 290 last week. Both the current total and the cumulative figure (7,725) are above the respective corresponding figures of any of the past 6 years.

Deaths recorded during the current week in 93 large cities of the United States totaled 9,171, as compared with 8,272 last week, 8,890 and 8,360, respectively, for the corresponding weeks of 1945 and 1944, and a 3-year (1943–45) average of 8,818. The total to date is 222,588, as compared with 216,604 for the corresponding period last year.

965 June 28, 1946

Telegraphic morbidity reports from State health officers for the week ended June 8, 1946, and comparison with corresponding week of 1945 and 5-year median

In these tables a zero indicates a definite report, while leaders imply that, although none was reported, cases may have occurred.

Division and State	Diphtheria			Influenza			Measles			Meningitis, meningococcus		
	Week ended—		Median 1941–45	Week ended—		Median 1941–45	Week ended—		Median 1941–45	Week ended—		Median 1941–45
	June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945	
NEW ENGLAND												
Maine	3	0	0	-------	-------	-------	203	3	113	0	1	1
New Hampshire	0	0	0	1	-------	-------	57	3	5	0	0	0
Vermont	0	5	0	-------	-------	-------	182	31	85	2	0	0
Massachusetts	1	4	2	-------	-------	-------	2,596	354	877	1	7	7
Rhode Island	0	0	0	-------	19	-------	138	11	11	0	1	1
Connecticut	0	1	1	1	1	-------	636	89	342	1	1	1
MIDDLE ATLANTIC												
New York	29	10	8	[1] 2	[1] 2	[1] 2	3,745	142	1,268	14	21	21
New Jersey	4	4	5	3	2	2	3,575	57	713	6	3	3
Pennsylvania	11	11	14	-------	1	-------	1,639	620	715	5	13	13
EAST NORTH CENTRAL												
Ohio	6	4	4	3	4	3	888	53	315	5	14	14
Indiana	2	1	3	3	13	1	192	49	73	1	0	1
Illinois	11	4	19	7	7	7	585	401	401	5	10	10
Michigan [2]	6	9	5	1	-------	-------	785	251	461	4	5	5
Wisconsin	3	0	1	22	21	20	1,776	155	1,431	3	5	3
WEST NORTH CENTRAL												
Minnesota	5	1	1	-------	-------	-------	93	17	309	1	1	1
Iowa	3	4	3	-------	-------	-------	244	63	97	0	1	0
Missouri	0	3	0	1	11	-------	108	45	185	4	6	6
North Dakota	1	1	1	-------	1	2	16	2	21	0	0	0
South Dakota	0	4	1	-------	-------	-------	12	36	14	0	1	0
Nebraska	0	2	2	-------	-------	1	152	105	89	0	1	0
Kansas	13	2	3	2	-------	-------	215	41	177	1	1	1
SOUTH ATLANTIC												
Delaware	0	0	0	-------	-------	-------	24	4	10	3	0	0
Maryland [2]	13	12	6	-------	1	1	717	25	204	1	0	8
District of Columbia	1	0	0	-------	-------	-------	137	2	60	0	1	1
Virginia	4	3	3	71	76	76	653	32	219	2	3	3
West Virginia	1	1	2	-------	-------	1	150	6	33	3	2	2
North Carolina	16	2	4	-------	-------	2	287	29	262	1	2	2
South Carolina	3	7	3	136	74	80	378	32	77	0	1	1
Georgia	2	4	3	7	5	6	64	4	37	1	4	2
Florida	5	1	2	2	-------	2	93	1	71	1	1	1
EAST SOUTH CENTRAL												
Kentucky	5	0	2	-------	-------	2	71	13	42	0	1	1
Tennessee	1	0	2	9	23	16	186	63	77	2	6	6
Alabama	5	4	2	23	9	14	157	5	71	3	5	2
Mississippi [2]	6	5	3	-------	-------	-------	-------	-------	-------	4	1	1
WEST SOUTH CENTRAL												
Arkansas	1	2	4	21	15	12	131	61	68	0	3	0
Louisiana	0	0	1	1	-------	1	34	52	21	0	0	2
Oklahoma	1	9	2	13	31	23	94	33	38	3	2	0
Texas	24	28	22	256	393	287	1,000	271	271	3	3	3
MOUNTAIN												
Montana	0	0	0	-------	3	3	153	7	43	1	0	0
Idaho	1	0	0	8	3	-------	58	2	29	0	0	0
Wyoming	0	0	0	-------	-------	-------	19	12	15	0	1	0
Colorado	4	7	8	3	63	22	303	10	151	0	0	0
New Mexico	1	2	1	1	-------	1	61	1	12	0	0	0
Arizona	3	1	1	32	33	33	138	11	64	0	1	1
Utah [2]	0	0	0	-------	-------	-------	212	212	112	0	1	1
Nevada	0	0	0	-------	-------	-------	1	4	13	0	0	0
PACIFIC												
Washington	6	4	3	-------	-------	2	116	193	223	0	4	2
Oregon	1	5	1	-------	7	7	205	89	89	1	0	2
California	27	11	16	8	13	42	1,762	1,458	1,458	11	9	9
Total	229	178	178	637	831	765	25,041	5,160	14,662	93	143	143
23 weeks	7,725	6,115	5,897	186,516	64,459	76,675	567,487	79,259	466,940	3,701	5,020	5,020

[1] New York City only.

[2] Period ended earlier than Saturday.

Telegraphic morbidity reports from State health officers for the week ended June 8, 1946, and comparison with corresponding week of 1945 and 5-year median—Con.

Division and State	Poliomyelitis			Scarlet fever			Smallpox			Typhoid and paratyphoid fever [3]		
	Week ended—		Median 1941–45	Week ended—		Median 1941–45	Week ended—		Median 1941–45	Week ended—		Median 1941–45
	June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945		June 8, 1946	June 9, 1945	
NEW ENGLAND												
Maine	0	0	0	18	38	13	0	0	0	1	0	0
New Hampshire	0	1	1	17	7	7	0	0	0	0	0	0
Vermont	0	0	0	3	10	5	0	0	0	1	0	0
Massachusetts	0	1	0	112	312	251	0	0	0	0	5	4
Rhode Island	0	0	0	3	5	8	0	0	0	0	0	0
Connecticut	1	0	1	28	45	43	0	0	0	0	1	1
MIDDLE ATLANTIC												
New York	6	11	4	398	526	344	0	0	0	4	7	7
New Jersey	0	0	0	155	112	112	0	0	0	1	1	2
Pennsylvania	3	1	0	209	412	219	0	0	0	5	4	6
EAST NORTH CENTRAL												
Ohio	4	0	0	224	336	229	0	1	1	1	4	4
Indiana	1	1	0	37	64	54	0	0	0	3	1	0
Illinois	4	2	2	173	205	146	1	0	0	2	1	2
Michigan [2]	0	0	0	115	234	178	0	0	0	2	1	2
Wisconsin	0	0	0	76	176	151	0	0	0	0	0	1
WEST NORTH CENTRAL												
Minnesota	3	0	0	45	77	40	0	0	0	0	0	0
Iowa	1	0	0	33	28	14	1	0	0	0	0	0
Missouri	2	0	0	12	44	44	0	0	0	1	0	1
North Dakota	0	0	0	0	18	6	0	0	0	1	1	0
South Dakota	0	0	0	8	26	8	0	1	0	0	0	0
Nebraska	0	0	0	9	28	17	0	0	0	0	0	0
Kansas	7	0	0	23	43	27	1	0	0	0	0	1
SOUTH ATLANTIC												
Delaware	0	0	0	0	3	4	0	0	0	0	0	0
Maryland [2]	0	0	0	68	125	39	0	0	0	1	1	1
District of Columbia	0	1	0	13	21	8	0	0	0	0	0	0
Virginia	0	2	0	43	65	20	0	0	0	2	0	3
West Virginia	1	1	0	20	36	18	0	0	0	1	2	2
North Carolina	* 2	2	0	16	41	17	0	0	0	1	3	3
South Carolina	3	3	1	11	12	4	0	0	0	10	1	1
Georgia	1	0	0	7	14	9	0	0	0	5	0	9
Florida	33	1	0	2	2	1	0	0	0	2	5	5
EAST SOUTH CENTRAL												
Kentucky	0	0	1	16	25	25	0	0	0	6	5	4
Tennessee	3	2	1	11	31	28	0	0	0	1	1	4
Alabama	15	2	1	10	13	11	0	0	0	4	9	1
Mississippi [2]	1	0	0	5	5	3	0	0	0	0	0	2
WEST SOUTH CENTRAL												
Arkansas	2	1	1	4	3	3	0	2	1	5	0	5
Louisiana	9	1	1	5	19	4	0	1	1	4	4	4
Oklahoma	2	1	1	5	23	10	0	0	0	1	1	3
Texas	35	42	1	25	40	26	0	0	0	13	9	9
MOUNTAIN												
Montana	0	0	0	5	10	10	0	0	0	0	0	0
Idaho	0	0	0	2	7	7	0	0	0	2	0	0
Wyoming	0	0	0	10	4	5	0	0	0	0	0	0
Colorado	5	0	0	18	38	38	1	0	0	1	0	0
New Mexico	0	0	0	3	6	3	0	0	0	1	2	2
Arizona	1	0	0	4	8	8	0	0	0	1	2	1
Utah [2]	0	1	0	17	11	11	0	0	0	0	0	0
Nevada	0	0	0	0	0	0	0	0	0	0	0	0
PACIFIC												
Washington	1	2	1	19	47	20	0	0	0	0	0	0
Oregon	0	0	0	26	17	12	0	1	1	0	1	1
California	15	13	9	150	326	173	0	0	0	5	8	3
Total	161	92	41	2,213	3,698	2,338	4	6	7	88	80	109
23 weeks	*1,195	903	586	77,487	120,416	87,636	236	224	514	1,268	1,401	1,790

[2] Period ended earlier than Saturday.
[3] Including paratyphoid fever reported separately, as follows: New York 1; Illinois 1; Michigan 1; Missouri 1; South Carolina 3; Georgia 2; Louisiana 3; California 1.
*Correction: North Carolina, week ended May 18, 1946, poliomyelitis, 2 cases (instead of 3).

Telegraphic morbidity reports from State health officers for the week ended June 8, 1946, and comparison with corresponding week of 1945 and 5-year median—Con.

Division and State	Whooping cough			Week ended June 8, 1946							
	Week ended—		Median 1941–45	Dysentery			Encephalitis, infectious	Rocky Mt. spotted fever	Tularemia	Typhus fever, endemic	Undulant fever
	June 8, 1946	June 9, 1945		Amebic	Bacillary	Unspecified					
NEW ENGLAND											
Maine	19	41	32								1
New Hampshire	5		2								1
Vermont	38	32	7								3
Massachusetts	100	171	171				1				
Rhode Island	28	16	27								
Connecticut	65	41	53								
MIDDLE ATLANTIC											
New York	145	210	241	3	6		1	1			9
New Jersey	184	112	122			1					1
Pennsylvania	63	166	215					1			2
EAST NORTH CENTRAL											
Ohio	72	130	130								2
Indiana	46	34	34								
Illinois	97	48	102	5	1		1		1		17
Michigan [2]	71	45	218	1	1						2
Wisconsin	100	26	125						1		5
WEST NORTH CENTRAL											
Minnesota	9	11	22	2							
Iowa	14		23								16
Missouri	13	29	29								1
North Dakota			8			1					
South Dakota			4								2
Nebraska	1		9								
Kansas	26	31	55						1		2
SOUTH ATLANTIC											
Delaware	1	1	1					1			
Maryland [2]	26	88	88					2			
District of Columbia	6	3	11					1			
Virginia	76	132	65			50					
West Virginia	17	11	23								
North Carolina	108	158	160					5		3	
South Carolina	67	75	79		68						
Georgia	5	21	27	1	3					14	7
Florida	27	8	10							7	3
EAST SOUTH CENTRAL											
Kentucky	33	23	55		1					1	1
Tennessee	25	33	51			1	1	1			
Alabama	45	67	55							5	2
Mississippi [2]									2	1	3
WEST SOUTH CENTRAL											
Arkansas		18	42	3					2		4
Louisiana		5	5				1			1	3
Oklahoma	8	9	9								
Texas	180	266	266	19	303	88				18	13
MOUNTAIN											
Montana	1	3	6								
Idaho	14	1	1	1				3			
Wyoming		2	7								
Colorado	19	40	29		1			1			1
New Mexico	10	6	7								2
Arizona	17	11	11	2		66					
Utah [2]	12	25	62						1		
Nevada			2								
PACIFIC											
Washington	29	17	60								
Oregon	20	24	20								
California	44	489	489	2	1		2	1		2	10
Total	1,886	2,679	3,778	39	385	207	7	17	8	52	113
Same week, 1945	2,679			40	556	172	7	15	12	97	95
Average, 1943–45	2,885			54	524	179	12	[4] 21	20	[4] 44	
23 weeks: 1946	42,905			897	7,597	2,710	200	105	400	1,067	1,973
1945	57,437			721	9,918	2,690	156	90	363	1,270	2,062
Average, 1943–45	64,066		[4] 88,081	694	7,183	1,945	223	[4] 106	345	[4] 1,061	

[2] Period ended earlier than Saturday.
[4] 5-year median, 1941–45.

Disease and Injury Surveillance

Introduction to Table V Premature Deaths, Monthly Mortality, and Monthly Physician Contacts — United States

MMWR 1982;31:109–10 (March 12, 1982)

Beginning with this issue, a new table will appear monthly in the MMWR: "Table V. Potential Years of Life Lost, Deaths, and Death Rates, by Cause of Death, and Estimated Number of Physician Contacts, by Principal Diagnosis" [see page 18]. By displaying a variety of measures that gauge the importance and relative magnitude of certain public health issues, this table will call attention to those issues where strategies for prevention are needed. Publication of this table reflects CDC's increased responsibility for promoting action to reduce unnecessary morbidity and premature mortality and continues the MMWR's tradition of disseminating public health information to its readership.

Further improvements in health can be achieved through actions taken by individuals as well as by administrators in the public and private sectors to promote a safer and healthier environment (*1*). To this end, the new table provides information regarding areas that provide the greatest potential for health improvement.

Causes of death are listed in Table V in descending order of the potential years of lost life that are attributed to each cause. In 1980, heart disease, cancer, and cerebrovascular disease account for 67.9% of all deaths in the United States; motor-vehicle and other accidents, suicide, and homicide accounted for 8.1% (*2*). In terms of age at the time of death, the relative importance of causes of death changes remarkably; motor-vehicle and other accidents, suicide, and homicide accounted for 40.8% of the total years of life lost prematurely (before age 65 years); and heart disease, cancer, and cerebrovascular disease accounted for 37.2%.

"Potential years of life lost before age 65" in the table is estimated for persons between 1 year and 65 years old at the time of death and is derived by multiplying the annual number of deaths in each age category by the difference between 65 years and the age at the mid-point of each category. If deaths of persons older than 65 years were included, greater weight would be given to natural causes of death, and premature and preventable causes of death would no longer be distinguishable. If deaths of persons younger than 1 year were included, causes of death affecting this age group would be weighted heavily and would therefore contribute a disproportionately large share of potential years of life lost. However, "Infant mortality" in the table is a measure of deaths occurring in this age group and "Prenatal care" reflects efforts to prevent death in this group.

Cause-specific mortality rates, published in the *Monthly Vital Statistics Report* by the National Center for Health Statistics, are estimated from a systematic sample of 10% of death certificates received in state vital statistics offices during a 1-month period using the underlying cause of death recorded on the certificate. Because complete information concerning the underlying cause of death is not available when the sample is taken, estimates for certain causes are biased in the monthly sample but then are corrected when annual estimates are made. The estimated number of deaths each month is obtained by multiplying the corresponding estimated mortality rate, which is computed on an annual basis, by the provisional population estimate for the

TABLE V. Potential years of life lost, deaths, and death rates, by cause of death, and estimated number of physician contacts, by principal diagnosis, United States, October 1981

Cause of morbidity or mortality (Ninth Revision ICD, 1975)	Estimated annual total of potential years lost before age 65, 1980[1]	Estimated monthly mortality[2]		Estimated number of monthly physician contacts[3]
		Number	Rate/100,000	
ALL CAUSES (TOTAL)	10,006,060	164,950	844.4	96,550,000
Accidents and adverse effects (E800-E807, E810-E825, E826-E949)	2,684,850	8,500	43.5	5,156,000
Malignant neoplasms (140-208)	1,804,120	36,120	184.9	1,990,000
Diseases of heart (390-398, 402, 404-429)	1,636,510	61,810	316.4	5,168,000
Suicides, homicides (E950-E978)	1,401,880	4,160	21.3	—
Chronic liver disease and cirrhosis (571)	301,070	2,730	14.0	100,000
Cerebrovascular diseases (430-438)	280,430	13,710	70.2	473,000
Pneumonia and influenza (480-487)	124,830	3,790	19.4	904,000
Diabetes mellitus (250)	117,340	3,130	16.0	2,764,000
Chronic obstructive pulmonary diseases and allied conditions (490-496)	110,530	4,280	21.9	1,824,000
Prenatal care[4]				2,187,000
Infant mortality[4]		3,700	11.7/1000 live births	

[1]National Center for Health Statistics. *Monthly Vital Statistics Report*, Vol. 29, No. 13, September 17, 1981. Total potential years of life lost are estimated for persons between 1 year and 65 years old at the time of death and are derived from the product of the number of deaths in each age category and the difference between 65 years and the age at the mid-point of each category.

[2]National Center for Health Statistics. *Monthly Vital Statistics Report*, Vol. 30, No. 11, February 10, 1982, pp 8-9. Infant deaths and provisional U.S. population from Vol. 30, No. 10, January 15, 1982, p 1. Mortality rates on an annual basis per 100,000 estimated population in the United States are estimated from the underlying cause of death recorded on a 10% systematic sample of death certificates taken from all those received in state vital statistics offices during a 1-month period. The number of deaths each month is estimated from the product of the corresponding estimated mortality rate and the provisional U.S. population estimated for that month divided by the number of days that month as a proportion of the total days in the year.

[3]IMS America. *National Disease and Therapeutic Index* (NDTI), Monthly Report, October 1981, Section III. This estimate comprises the number of office, hospital, and nursing home visits and telephone calls prompted by each medical condition based on a stratified random sample of office-based physicians (2100) who record all private patient contacts for 2 consecutive days each quarter.

[4]"Prenatal care" and "infant mortality" are included in the table because "Potential years of life lost" does not reflect deaths of children <1 year.

United States and then dividing by the number of days for that month as a proportion of the total days in the year.

The measure for morbidity is obtained from the National Disease and Therapeutic Index (NDTI), a random sample of data from office-based physicians in 19 major specialities in the continental United States. Each physician in the sample records all his contacts with private patients for 2 consecutive days each quarter. These contacts comprise telephone calls (7% of total in 1981); office visits (68%); and patients visited by the physician in hospitals (22%), nursing homes (1%), and their own homes (1%). As a result, this measure gives greater weight to those diseases that prompt a visit to a private physician or required hospitalization. When the physician cannot make a diagnosis at the time of the visit, the suspected diagnosis or presenting symptom is recorded. Although misclassification might occur, the potential for this bias is reduced by using broad categories in the table.

Publication of Table V is an effort to use measures of morbidity and mortality as reminders of the impact on public health of some of these preventable problems. However, when data are summarized, their complexity and detail are sacrificed; and when information is simplified, although the overall effect may be clarified, subtle issues may be obscured. Therefore, a series of articles exploring different aspects of preventable problems will be published in the MMWR to complement this table. These articles will present more detailed analysis of what is known about health status indicators, risk factors, and other factors affecting public health.

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Editorial Note—1997

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The 1982 addition to the *MMWR* of a monthly Table V, "Premature Deaths, Monthly Mortality, and Monthly Physician Contacts—United States," employed the measure of years of potential life lost (YPLL), which was designed to alert the public health community to the magnitude of "premature," "preventable," and "unnecessary" mortality. In contrast to the traditional measures of crude and age-adjusted mortality, which treats deaths at all ages equivalently, YPLL weights deaths inversely to age at death (i.e., deaths at young ages affect the value of YPLL more than deaths at older ages). Although the measure had been used since 1947 (*1*), the CDC series on YPLL especially raised awareness about the magnitude of the problem of injury among youth (*2*), causes of death among infants (e.g., sudden infant death syndrome [SIDS] and congenital anomalies [*3,4*]), and acquired immunodeficiency syndrome (AIDS) (*5*). YPLL contributed to the establishment of CDC's Violence Epidemiology Branch in 1983 and CDC's National Center for Injury Prevention and Control in 1992. Other measures of years of life lost have been modified to account for the "quality" of life lived with different types of morbidity and disability. For example, years of healthy life (YHL) considers activity limitations and perceived health and has been used to estab-

lish and monitor national health objectives in the United States for the year 2000 (*6*). In addition, disability-adjusted life years (DALY) "expresses years of life lost to premature death and years lived with a disability of specified severity and duration" (*7*). Measures of YPLL have served primarily as tools for health-care planning, prioritization, and administration rather than as instruments of causal research.

An analysis of "potential years of life lost" was first published 50 years ago by Mary Dempsey (*1*), a statistician at the National Tuberculosis Association, who sought to indicate the relative youth of decedents from tuberculosis compared with cancer and heart disease; while crude mortality rates of the latter were far higher, YPLL rates were more comparable. Many modifications and alternatives to YPLL have been formulated (*8,9*). Dempsey used life-expectancy-at-birth cutoffs specific to the populations compared; in contrast, some have used a fixed life expectancy for all populations compared, as proposed by Haenszel (*10*). Others have used different age cutoffs, at both lower age limits (e.g., 0, 1, 15, and 20 years) and upper limits (e.g., 65, 70, 75, and 85 years). The measure including ages 15–70 years has been referred to as potentially productive years of life lost, on the assumption that these are the productive years of life (*9*). Another measure, years of accumulated ability lost (YAAL), weights the number of deaths by the age at which they occur, on the assumption—contrary to that made in YPLL—that the potential contribution of the decedent is greater with greater age and experience; YAAL may be regarded as the inverse of YPLL (*11*).

YPLL measures the burden of mortality among the relatively young. As a rate (generally calculated per population aged <65 years), YPLL could be compared by cause (e.g., injury, AIDS, and cancer) or etiologic agent (e.g., cigarette smoking, alcohol consumption, and automobiles), among populations (e.g., by sex, race/ethnicity, and state), and over time. Although YPLL rates may be age-adjusted, adjustment may mask differences in the public health burden of mortality among youth, which YPLL measures.

YPLL can be interpreted in at least two ways. First, as indicated by its name, YPLL may be regarded as the sum of years of life lost by persons who died before age 65 years; thus, for example, a person who died at age 24 years lost 41 years of life, assuming he or she would have lived to be only 65. Second, assuming that young persons have greater life expectancy than older persons and that death at young ages is therefore a greater loss than death at older ages, YPLL can be interpreted as a measure of mortality in which death at young ages is numerically weighted more heavily than death at older ages. For example, the death of a 5-year-old has a weight of 60 (i.e., 65 minus 5 years), 12 times the weight of 5 for a 60-year-old who dies (i.e., 65 minus 60 years).

The measure of YPLL reported in the *MMWR* has been modified in several ways over the course of its publication. Until 1986, deaths among infants (aged <1 year) were excluded from YPLL calculations in the *MMWR* because it was believed that they would "be weighted heavily and would therefore contribute a disproportionately large share of potential years of life lost" (*12*). In 1986, deaths during the first year of life were added to the calculation, and infant mortality was no longer reported separately in Table V (*13*). This change resulted in the addition of congenital anomalies, prematurity, and SIDS as the fifth, sixth, and seventh causes of YPLL, respectively. Also beginning in 1986, YPLL tables and analyses were published annually rather than more frequently. In 1990 and 1992, annual *MMWR* reports on YPLL included comparison of YPLL with an upper age cutoff of 85 years in addition to the standard cutoff of

65 years (*14,15*). Initially, the nine leading causes of YPLL were reported; in the last years of publication, 13 leading causes were reported. While all-cause YPLL has declined slightly since the mid-1980s, this overall decline has been offset by an 11-fold increase in the proportion of YPLL associated with AIDS, first reported for 1984. In 1993, YPLL estimates based on provisional mortality data were not compared directly with estimates based on final data because of cause-specific differences in the delay of reporting provisional data (*16*). In 1986, a widely cited *MMWR* supplement, *Premature Mortality in the United States: Public Health Issues in the Use of Years of Potential Life Lost*, was published to review alternative methods for the estimation of potential life lost (*8*).

The limitations of YPLL measures may constrain, in part, their usefulness. First, although YPLL has been thought to measure premature, preventable, and unnecessary morbidity and mortality, this assumption has not been evaluated and depends on the current state and deployment of knowledge and prevention strategies. Second, many YPLL measures ignore a large proportion of deaths in the population, including, for example, all deaths among persons aged ≥65 years. In 1994, 73% of deaths in the United States occurred among persons aged ≥65 years, and 24% occurred among persons aged ≥85 years (*17*). Many measures neglect the potential for premature, preventable, and unnecessary morbidity and mortality among persons in these age groups.

An annual report on changes in YPLL was last published in *MMWR* in 1993 (*16*), although YPLL statistics have been routinely published in CDC's annual compendium *Health, United States* (*18*), and CDC programs continue to report condition- and etiology-specific YPLL in *MMWR*. CDC is reviewing its policy on how best to routinely disseminate age-related mortality information to achieve public health objectives. In addition to concerns about age-related value assumptions, there is growing interest in incorporating into summary health measures assessments of the "quality" of years lived or lost, the morbidity and disability associated with given causes of death before death, and self-perceived health status. These measures are intended to be used for surveillance and to provide a common denominator for cost-utility analysis. In addition, the importance of notions of premature, preventable, and unnecessary morbidity and mortality should be related to effective clinical and public health practice.

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Public Health Focus: Effectiveness of Disease and Injury Prevention

MMWR 1992;41:265–6 (April 24, 1992)

Public health practice is based on scientifically sound strategies for improving the quality of life and reducing morbidity and premature mortality. To maximize the health benefits of available resources, public health decision-makers require information on the effectiveness, as well as the economic and social impact, of disease and injury prevention strategies (*1*). This report introduces a monthly series of articles to be published in *MMWR* (weekly) that highlight prevention effectiveness.

The development of prevention technology begins with researchers in the basic public health and biomedical sciences identifying potentially effective technologies that can be used to reduce unnecessary morbidity and premature mortality. Applied research under carefully controlled conditions may then determine whether such techniques are efficacious (e.g., the effect of smoking cessation on lung cancer). As these techniques are applied at the community level, their impact and cost can be assessed first in demonstration settings and then in routine community settings, and improvements in techniques can then be incorporated into prevention strategies.

Important considerations in the assessment of disease and injury prevention strategies (i.e., the scientific method for evaluating the effectiveness of prevention strategies) include

- identification of efficacious and effective strategies to reduce morbidity and premature mortality and improve the quality of life;
- characterization of the social, legal, and ethical impact of these strategies;
- estimation of the economic impact of prevention strategies;
- determination of optimal methods for implementing those strategies; and
- evaluation of the health impact of prevention programs.

Each report in the monthly series will highlight the knowledge base regarding a specific prevention strategy and will address related considerations, including efficacy, effectiveness, safety, and economic factors. Topics have been selected based on their inclusion in the national health objectives for the year 2000 (*2*), CDC and other public health program efforts, and the availability of data. In particular, the reports will present specific examples of disease and injury prevention strategies and illustrate approaches to evaluating the effectiveness of such strategies.

Reported by: Office of Program Planning and Evaluation, Office of the Director; Office of the Director, Epidemiology Program Office, CDC.

Editorial Note: Public health officials and policy-makers at all levels require a scientific framework for assessing the effectiveness of disease and injury prevention as a basis for establishing priorities, selecting prevention strategies, and allocating resources. The success of prevention activities can be defined by whether they delay or avert morbidity and mortality. However, the ability to evaluate objectively many prevention techniques with randomized controlled trials is often limited by fiscal, ethical, or other constraints. The *MMWR Recommendations and Reports* issue, "A Framework for Assessing the Effectiveness of Disease and Injury Prevention" (*1*), focuses on the

challenges of assessment that arise as a consequence of these constraints. Reports in the *MMWR* (weekly) series will describe examples of how prevention effectiveness can be assessed.

Because public health programs sometimes may begin to implement preventive measures before appropriate assessments are completed, gaps may exist in knowledge of the efficacy, effectiveness, safety, or economic impact of specific prevention strategies. The series of reports in *MMWR* (weekly) will characterize many of these gaps and describe how they have been addressed. In addition, the reports in this series are intended to 1) provide decision-makers with information about the potential impact of these interventions on the health of their communities; 2) suggest approaches suitable for adaptation to public health practice; and 3) encourage further examination of these topics and stimulate additional systematic efforts by public health professionals to assess and enhance the effectiveness of public health programs.

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Editorial Note—1997

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Since the initiation of the series of articles (*1–7*) and publication of the *MMWR Recommendations and Reports* (*8*) on prevention effectiveness, the concepts have been institutionalized as a public health science at CDC and many other organizations in the public health community. Public health programs traditionally have been accountable for their effectiveness and have had to exist within resource constraints. Choices among competing priorities and intervention strategies have been and will continue to be made regardless of the information available. Prevention effectiveness integrates the best available information into the value of those choices.

The prevention-effectiveness initiative has helped to catalyze the integration of the principles of evidence-based medicine (*9*) into public health. A central feature of this approach is the focus on health outcomes. By examining the links between interventions, intermediate impacts, and health outcomes, synthetic analyses can be developed as tools to assist in selecting the best intervention strategies. These tools assist in clarifying the objectives, the strategies available to achieve those objectives, the logic of the causal pathways, and the evidence that supports the links in those pathways. In addition to facilitating understanding of problems and potential solutions, these tools provide a basis for developing practice guidelines (*10*) and, in the future, adapting those guidelines to communities with differing demographics, risk profiles, and health concerns (*11*).

Public health uses clinical interventions as well as behavioral, environmental, and social approaches. Many of the prevention-effectiveness methods that have been applied in the clinical arena (e.g., decision analyses and economic evaluations as applied to technology assessments, outcomes research, and health services research)

needed to be adapted to public health. Recommendations for comparable methods for decision modeling and analysis and economic evaluation in public health are now available (*12,13*). These standards for analysis assure policymakers that studies conducted in accordance with these principles are reliable and comparable.

The need to spend limited health-care resources more efficiently is generally accepted. Managed-care and public health partners now routinely explore the broadest range of community-based intervention strategies to improve the health of the populations they serve. The tools of prevention effectiveness provide decision-makers with critical information necessary for improving decision-making to weigh along with ethics, feasibility, and the distribution of costs and benefits to different populations. For example, policy discussions on the fortification of food with folic acid to reduce neural tube defects used economic evaluations to compare the costs, benefits, and hazards associated with fortifying foods with different levels of folic acid, with diet supplementation, or with no intervention (*14*).

Since 1992, CDC has increased substantially its capability in prevention effectiveness through courses, postdoctoral fellowships, routine use of economic evaluations (cost-effectiveness and cost-benefit and cost-utility analyses), and the development of comparable methodologies (*11*). For example, a recent study of the cost-effectiveness of antibiotics for the treatment of chlamydia cervicitis (*15*) led to a negotiated public health price for a single-dose formulation of azithromycin suitable for administration in clinics. Prevention effectiveness has become a core science for public health, but additional efforts are required to clarify understanding of how prevention-effectiveness studies can be better used by decision-makers. Methods for measuring outcomes (such as quality-adjusted life-years and benefits estimation for cost-benefit analyses) and resource allocation need to be refined. Finally, improved, more complete, and comparable information on cost-effectiveness needs to be available to users.

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Addition of Prevalence of Cigarette Smoking as a Nationally Notifiable Condition — June 1996

MMWR 1996;45:537 (June 28, 1996)

On June 6, 1996, by a unanimous vote, the Council of State and Territorial Epidemiologists (CSTE) added **prevalence of cigarette smoking** to the list of conditions designated as reportable by states to CDC. The addition of prevalence of cigarette smoking marks the first time a behavior, rather than a disease or illness, has been considered nationally reportable.

Goals of smoking prevalence surveillance identified by CSTE include monitoring trends in tobacco use, guiding allocation of tobacco-use prevention resources, and evaluating public health interventions to reduce smoking. Given these goals, CSTE selected population sampling as the appropriate surveillance methodology and designated the Behavioral Risk Factor Surveillance System (BRFSS) as the preferred data source. CSTE and CDC are developing the format to regularly present this information in national disease reporting statistics. The addition of cigarette smoking prevalence brings to 56 the number of diseases and conditions designated by CSTE as reportable by states to CDC.

Reported by: Council of State and Territorial Epidemiologists. Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion; Div of Surveillance and Epidemiology, Epidemiology Program Office, CDC.

Editorial Note: National notifiable disease surveillance has been critical to the successful campaign against infectious diseases throughout this century. By agreement among states, CSTE, in partnership with CDC, determines the list of conditions reportable to CDC. The addition of prevalence of cigarette smoking to this list is a historic step in the evolution of the public health surveillance in the United States.

Although most conditions reportable by states to CDC have been acute infectious diseases, and surveillance for such diseases remains a public health priority, the addition of prevalence of cigarette smoking reflects shifts in morbidity and mortality patterns in the United States and therefore the need to expand the range of nationally reportable conditions. Traditionally, infectious disease reporting has relied on a single methodology—mandated reporting of all cases. The decision by CSTE to designate BRFSS as the recommended data source for reporting of this condition marks a transition to a more flexible system in which surveillance methods are determined by surveillance goals. Most importantly, this action underscores the role of tobacco use as the leading preventable cause of death in the United States and the need to conduct national public health surveillance for both conventional disease outcomes and for underlying causes (e.g., smoking and other risky behaviors) amenable to public health intervention (*1*).

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INFECTIOUS DISEASES

Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:172 (May 24, 1963)

Sweden — Stockholm was declared a smallpox infected area on May 16. A seaman who returned from Indonesia in late March is the apparent source of an outbreak which has now spread through two generations of transmission and has resulted in one fatality. Preliminary information on cases to date, received from the Ministry of Health, Sweden, and forwarded by Dr. Reimert T. Ravenholt, Epidemiologic Consultant, Division of Foreign Quarantine, U.S. Public Health Service, Paris, is given below:

The outbreak was recognized on May 13 when the diagnosis of smallpox was first suspected in Case #7. The disease was sufficiently mild in Cases 1, 4, 5 and 12 that medical assistance was not sought. The only fatality to date occurred in Case #2 who apparently suffered an acute hemorrhagic form of the disease, diagnosed as smallpox in retrospect.

This outbreak is of unique interest in that it represents one of the few epidemics in Western nations in recent years not evidencing a predominant spread among hospital contacts. Recent immunization programs among hospital personnel presumably have altered the pattern of hospital spread observed in other recent outbreaks. The mildness of the disease in several of the earlier cases, resulting in the failure of these patients to seek medical care and hospitalization, has contributed to the pattern of community transmission.

The outbreak emphasizes the sinister role of mild or vaccine-modified cases of smallpox in initiating and propagating outbreaks of severe disease. Since the outbreak was discovered during the second generation of indigenous cases, it is possible that Americans recently in Stockholm have been unknowingly exposed to the disease, and cases of suspicious febrile illness in such individuals should receive the utmost scrutiny by clinicians and public health authorities.

Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:174–6 (May 31, 1963)

Four additional cases of smallpox have been identified in Stockholm with onsets of illness since May 18. All four presumably acquired their disease as a result of hospital contact.

The outbreak (See MMWR, Vol. 12, page 172) now totals 16 cases, with three generations of transmission following the importation of smallpox by a seaman who presumably acquired his disease in transit through Southeast Asia. Information on cases to date received from Dr. Bo Zetterberg, Chief, Epidemiology Division, State Bacteriology Laboratory, Stockholm, is summarized in the table below [See table, page 32].

The pattern of spread of the illness is presented diagrammatically in the accompanying figure [See figure, page 33].

The first case to be identified occurred in an unvaccinated 19-year-old bricklayer (Case 7) who had onset of fever, vomiting, and backache on May 5. He was hospitalized three days later and subsequently developed an extensive maculo-papular rash

SMALLPOX — STOCKHOLM
Summary of Current Information on Cases

Case No.	Age	Sex	Date of Onset	Presumed Source of Infection	Last Vaccination	Comment
1	24	M	April 6	Southeast Asia	1959	Modified illness
2	58	F	April 18	Case #1	Childhood	Died April 23
3	80	F	April 21	Case #1	Childhood	
4	24	F	April 25	Case #1	1943	Modified illness
5	20	F	Not known	Case #1	1950	No rash (Lab diagnosis)
6	53	M	May 3	Case #2	1920	Husband of Case #1
7	19	M	May 5	Case #2	Never	Died May 28
8	50	F	May 5	Case #3	Childhood	Home Nurse of Case #3
9	55	F	May 5	Case #3	1916	Home Nurse of Case #3
10	67	F	May 6 or 9	Case #3	1918	
11	72	F	May 8	Case #3	1915	No known direct contact
12	22	M	May 11	Case #4	1961	Laboratory diagnosis only
13	61	M	May 18	Case #3 or 6	1949**	Hospital acquired
14	1½	F	May 19	? Case #6	Never**	Hospital acquired
15	72	F	May 24	Case #9	Childhood	Hospital acquired–Died May 27
16	75	F	? May 24	Case #9	Childhood	Hospital acquired

*First identified case.
**Revaccinated within 8 days of onset.

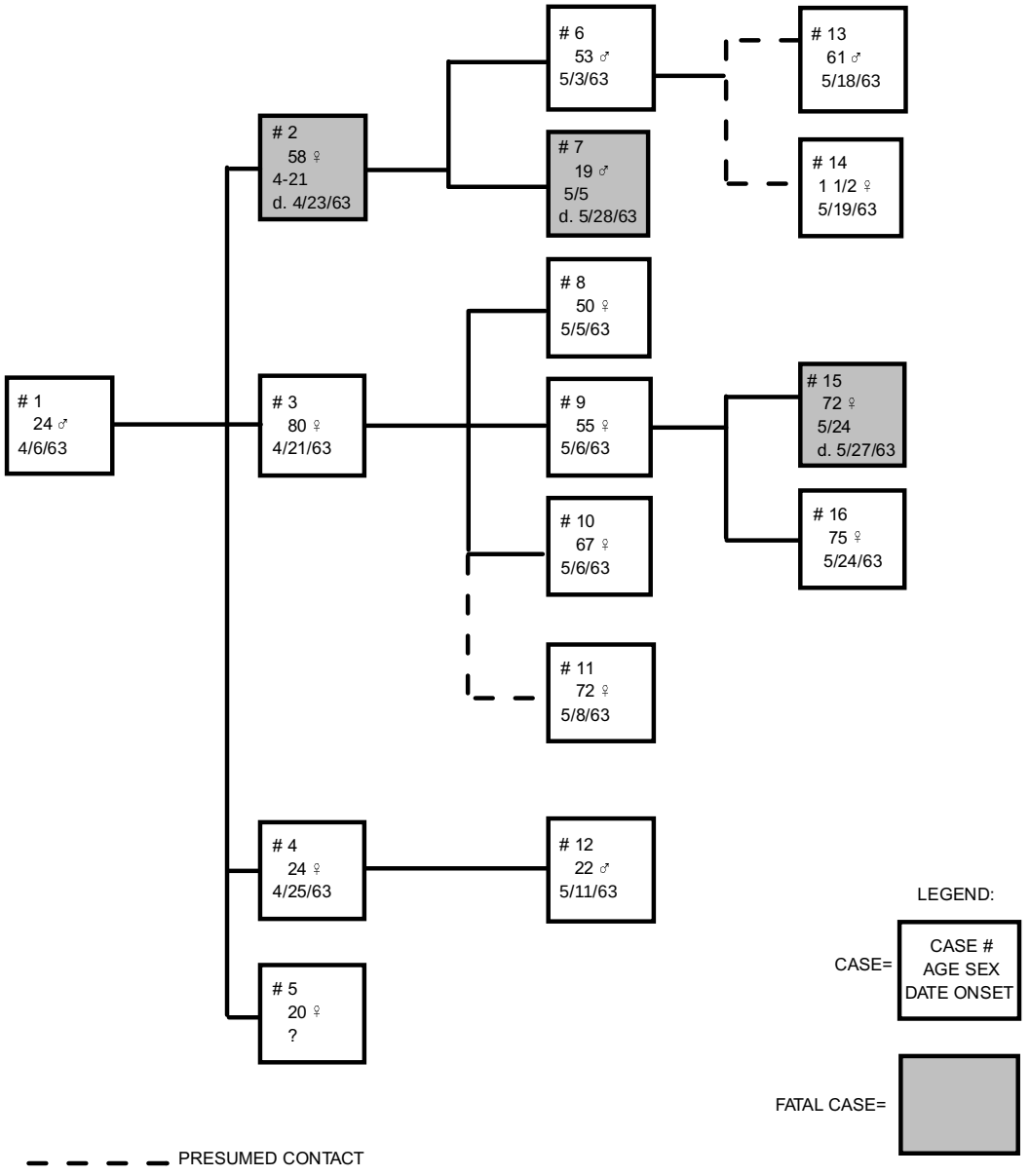
which became pustular by May 12. Smallpox was suspected and confirmed the following day by the laboratory.

Immediate epidemiologic investigation revealed that an aunt of the bricklayer (Case 2) had developed on April 18 an acute febrile illness, manifest by hemorrhagic skin lesions, and had died shortly after admission to the hospital on April 23. Ten other cases of smallpox were identified May 14–16.

The original source of the outbreak was a 24-year-old seaman who after two weeks residence in Australia left Darwin on March 22 on BOAC Flight #709. In-transit stops of not more than 50 minutes each were made in Djakarta, Singapore, Rangoon, Calcutta, Karachi, Teheran, and Damascus en route to Zurich. At Zurich, the seaman deplaned and the following day boarded Swissair Flight #250, reaching Stockholm March 24. He apparently acquired his disease as a result of in-transit exposure either at a terminal or on the plane. On April 6, 15 days after the flight, he developed a moderate fever and mild rash and remained in the home of his grandmother (Case 3) throughout his illness. Cases 2, 3, 4, and 5 all had contact with him in the grandmother's home during the course of his illness. On April 21, the grandmother fell ill, subsequently exposing three women (Cases 8–10) who visited the home to provide nursing care to the elderly woman prior to her hospitalization on May 27. She was originally diagnosed as having chickenpox and recovered uneventfully. Another resident of the building (Case 11) who lived two stories above the grandmother, developed smallpox but denied acquaintance or contact with the grandmother.

Case 2, the first fatality, apparently acquired the illness from the seaman during a visit to the grandmother's apartment and subsequently transmitted it to her husband

SMALLPOX - STOCKHOLM - 1963
DIAGRAMMATIC REPRESENTATION OF THE OUTBREAK



(Case 6) and her nephew (Case 7) the first identified case. Case 12 who had only fever and serologic evidence of infection, acquired his disease presumably from his fiancee, Case 4.

The appearance of cases among hospital contacts is more consistent with the previously observed patterns of imported smallpox in Western countries. Case 13 is a gardener at the Infectious Disease Hospital where Cases 3 and 6 were admitted as presumptive chickenpox on April 27 and May 7, respectively. He is thought to have

handled laundry from these patients prior to the first suspicion of smallpox on May 12. He was initially employed by the hospital only two months previous and had not yet been vaccinated in the hospital's annual revaccination program.

Case 14 was a patient admitted to the Infectious Disease Hospital with whooping cough on April 30. She was located in the same hospital vicinity as Case 6, although there was no connection between the rooms housing these patients. Cases 15 and 16 were patients on the same hospital ward to which Case 9 was admitted on May 9. Case 9 was originally thought to have a toxic drug eruption prior to her diagnosis of smallpox on May 15.

With the exception of Case 12 who had an exceptionally mild illness, it is apparent that spread of the disease to date has been primarily among individuals vaccinated at times far distant in the past. Of the three fatalities to date, one occurred in a person never vaccinated and the other two in persons vaccinated more than 50 years prior to exposure. The absence of additional spread to hospital personnel is probably related to efforts in Sweden to emphasize revaccination of hospital personnel at frequent intervals. Notably, the last four cases have occurred in persons already identified and isolated by virtue of being known contacts.

Some 8,000 persons living in neighborhoods of the earlier cases have been vaccinated. In addition, vaccination has been provided for other residents of Stockholm on request and to date some 300,000 persons have availed themselves of this protection.

Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:183,188 (June 7, 1963)

Three additional cases, two hospital acquired, were identified last week bringing to 19 the total number of smallpox cases comprising the current outbreak, according to information made available by Dr. Bo Zetterberg, Chief, Epidemiology Division, State Bacteriology Laboratory, Stockholm.

Two of the three cases are actually part of the second generation of transmission (See MMWR Vol. 12, pg. 174), having now been identified retrospectively by serologic means. Neither patient developed a rash. Both were nurses in the Stockholm Infectious Disease Hospital in close contact with the smallpox cases admitted there. The first, a 44-year-old female, cared for Case No. 3 from April 27 to May 7 daily, including bathing and local treatment of the lesions. On May 9, the nurse developed fever and headache, as well as nausea and low back pain. Except for May 13 and 14, she continued to work throughout her illness until isolated on May 18. She was found to have a very high hemagglutination inhibition antibody titer suggesting recent infection. Her last vaccination prior to onset of illness was in 1962. She was also in daily contact with Cases 6 and 14, and directly or indirectly may have transmitted the disease to Case 14.

The second nurse, a 22-year-old female, also employed in the Stockholm Infectious Disease Hospital, had daily contact with Case No. 2 during the period April 27–May 7. On May 11, she experienced onset of headache, fever, and sore throat and was absent from work May 11 through May 13. No rash developed. A high HAI titer verified the diagnosis of smallpox. She had previously been vaccinated in 1950 but at the time of exposure had not yet been revaccinated under the hospital's annual revaccination program.

The final additional case is that of a 47-year-old man who had onset of illness May 21 while already isolated as a contact. He is the father of Case 7, the first identified case. He had never been vaccinated until 7 days before onset of illness.

The total number of hospital-acquired cases now stands at 6, one-third of the secondary indigenous cases. The evidence supports close contact as the primary requisite for spread both in the hospital and in the community. The disease has spread among persons vaccinated more than 7 years prior to the time of their exposure with 2 notable exceptions, both patients with mild disease without rash. The table below presents data on the vaccination status of the 18 indigenous cases [See table below].

Time Lapse Since Last Vaccinated	Indigenous Cases	Clinical Characteristics		Deaths
		Rash	No Rash	
7 yrs. or less	2	–	2	–
8–14 yrs.	3	1	2	–
15–24 yrs.	2	2	–	–
25–50 yrs.	4	3	1	–
More than 50 years	4	4	–	2
Never	3	3	–	1
Totals	18	13	5	3

Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:191,196 (June 14, 1963)

Two additional cases of smallpox were identified in Stockholm last week bringing to 21 the total number of cases in the current outbreak. Unique circumstances involving these two persons, neither of whom were under surveillance as contacts at the time of their detection, indicates that the outbreak may perhaps be expected to continue.

Information made available by Dr. Bo Zetterberg, Chief, Epidemiology Division, State Bacteriology Laboratory, Stockholm, indicates that on June 6 an 85-year-old woman, who lives with her daughter, went to a hospital out-patient department for routine follow-up of a chronic medical problem. The daughter called in advance informing clinic personnel that the elderly woman had developed a rash. On arrival at the out-patient clinic, the mother spent some time in the general waiting room and was then referred to the dermatology clinic, and again spent some time in the dermatology waiting room. When seen by physicians, a clinical diagnosis of smallpox was made. In all, she had spent some four hours at the hospital and presumably exposed some 450 persons in the two crowded waiting rooms. It was noted that on May 28 she had developed a low-grade fever with dizziness, followed by the appearance of rash on June 2.

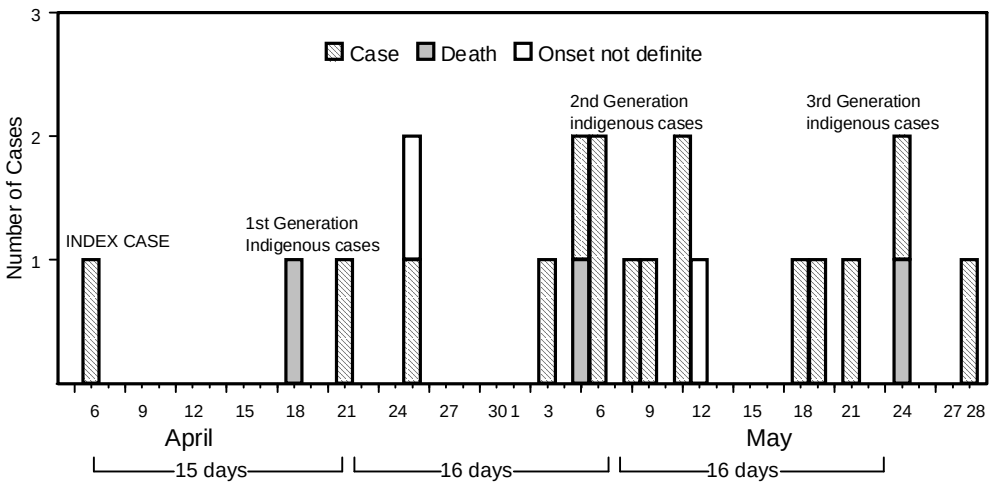
She and her 54-year-old daughter share an apartment in a boarding house for women housing some 100 occupants. The daughter works as a mortician and on April 26 had prepared the body of smallpox Case 2 of the outbreak for cremation. She had been placed under surveillance as a contact and 16 days after her exposure to the dead woman, having had no symptoms or signs of illness, she was released from

quarantine. She denied any evidence of illness since being released from surveillance. The total elapsed time from her contact with the body of Case 2 and the onset of disease in her mother was 32 days, consistent with two incubation periods of smallpox. Except for the daughter's exposure, no epidemiologic evidence could be found linking the mother with a source of smallpox. Neither the mother nor daughter had been vaccinated since childhood. The daughter demonstrated a high HAI titer on June 6, suggesting a recent infection, and in the absence of an alternative explanation, it may be presumed that the daughter developed a sub-clinical infection and transmitted virus to her mother. Two very unusual aspects of smallpox transmission seem apparent. The daughter, unvaccinated since childhood and exposed to hemorrhagic smallpox, developed an infection so mild as to produce no symptoms, yet developed serologic evidence of infection. Despite the presumed absence of any rash or systemic manifestations of disease, she was apparently able to transmit the illness to her mother.

The inadvertent exposure of the mother during her eruptive stage to some 450 persons at the hospital, as well as possible contacts in the boarding house, establishes an additional large group of contacts in which cases may yet occur.

An epidemic curve for the outbreak to date is presented showing the chronologic relationship of the generations of transmission [See Figure below]. Using the median date in the span of onset dates for each generation, it is apparent that the median incubation periods for all generations are strikingly similar.

SMALLPOX - STOCKHOLM
EPIDEMIC CURVE BASED ON DATE OF ONSET OF ILLNESS



Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:220 (July 5, 1963)

No new cases have been reported during the past week. The total number of confirmed cases remains at 23, including four deaths. The fourth death reported involved an unvaccinated 47-year-old male who died on June 15, 25 days after onset of illness.

He was the father of case 7, also a fatality (See MMWR, Vol. 12, No. 21, pp. 174 and 183).

Smallpox — Stockholm, Sweden, 1963

MMWR 1963;12:236 (July 19, 1963)

Two additional cases of smallpox were reported from Stockholm on July 11 and July 12, respectively. One of these, an 89-year-old female patient in a mental hospital, had onset of rash and fever on July 7, 15 days after onset of illness in Case 23, a 73-year-old woman also hospitalized at this institution.

The total number of confirmed cases that has occurred during the outbreak is 25, including four deaths.

Editorial Note—1996

Donald R Hopkins, MD, MPH, Carter Center/Global 2000, Atlanta, and former Deputy Director, CDC. J Donald Millar, MD, DTPH (London), President, Don Millar & Associates, Inc., Atlanta, and former Director, National Institute for Occupational Safety and Health, Center for Environmental Health, Bureau of State Services, and Smallpox Eradication Program, CDC.

Reading this *MMWR* account of the outbreak of imported smallpox in Sweden during April–July 1963 is as haunting now as it was frightening then. At the time, there was justifiable concern about possible spread of infection from Sweden to the United States, and when residents of Stockholm were offered vaccination during the outbreak, "some 300,000 persons...availed themselves of this protection."

Sweden was the first major country to eliminate indigenous smallpox, a distinction it achieved in 1895 (*1*). This outbreak was the first appearance of imported smallpox there since 1932, except for a single case in 1945 (*2*). Infecting 25 persons over six indigenous generations of transmission, this was one of the larger such outbreaks in Europe (which had two other imported outbreaks in 1963, four in 1962, and 10 in 1961, for example) after 1958 (*3*). Despite Sweden's active vaccination efforts among hospital personnel, eight of the indigenous cases were acquired by hospital staff or patients; most of the remainder were infected by face-to-face contact in the homes of case-patients. However, the versatile virus apparently also spread in this one outbreak from a corpse, from laundry of another case-patient, and by remote airborne exposure, and its clinical presentation ranged from six cases (among persons with old vaccinations) who did not develop a rash at all to at least one hemorrhagic case.

Several aspects of the outbreak in Sweden differed dramatically from smallpox outbreaks in Great Britain the previous winter following importations from Pakistan. In particular, this outbreak was not recognized until seven cases already had occurred; ambulatory cases with "mild" disease were important in early transmission; the overall case-fatality rate was substantially lower (15% in Sweden versus 40% in Great Britain). At the time, these differences were attributed to vaccine-modification of smallpox associated with the ameliorating influence of partial immunity from distant prior vaccinations. In retrospect, they may reflect infection with a strain of smallpox virus from Indonesia where smallpox historically seemed to be less lethal than on the Indo-Pakistan subcontinent.

In the outbreak in Sweden, hospital transmission of smallpox was not prominent in the early generations of disease as it was in most other European outbreaks associated with importation. However, once patients began to be admitted to the hospital, the hospital became the focus of transmission. In addition, transmission also was associated with contact with fatal cases; indeed, handling smallpox corpses and attending funerals of smallpox victims resulted in outbreaks in Africa and other smallpox-endemic areas during the global smallpox eradication campaign (*4*).

Dr. Ronald R. Roberto, an officer in CDC's Epidemic Intelligence Service Program during 1962–1964, went to Stockholm as an international observer during this outbreak. In addition to his role in rapidly communicating emerging information to CDC, he formed relationships with Swedish colleagues—including epidemiologists H. B. Lundbeck and B. O. Ringertz and virologist J. A. Espmark—who made important contributions to the subsequent development of smallpox eradication activities of CDC and the World Health Organization.

This outbreak also highlights how interconnected the world was already in 1963, and it illustrates vividly the potential danger posed to all other humans as long as smallpox existed anywhere on the planet. Even discounting the unknown, apparently chance encounter by which the index patient in this outbreak came to be infected, the capricious nature of many of the subsequent encounters that resulted in indigenous cases in Sweden is breathtaking. The painful lesson was not lost on Sweden, which contributed almost $16 million to the global Smallpox Eradication Program, beginning in 1967, making it the second largest donor after the United States (*3*). Sweden's generosity was especially important during the final battles against smallpox in India, Bangladesh, and Somalia.

Finally, it is fitting that CDC marks the 50th Anniversary of its own founding by commemorating the 200 years since Edward Jenner discovered vaccination in May 1796 and the 30 years since the Nineteenth World Health Assembly resolved in May 1966 to eradicate smallpox over the next 10 years. The CDC effort in helping 20 West and Central African countries to eradicate smallpox early in the global campaign with support provided by the U.S. Agency for International Development and by the Public Health Service remains one of its finest and most beneficial achievements.

The glorious legacy of the global Smallpox Eradication Program lives today in the campaigns to eradicate dracunculiasis and poliomyelitis. Others too will follow.

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Smallpox Surveillance — Worldwide

MMWR 1978;27:8 (January 6, 1978)

A total of 3,234 cases of smallpox have been reported from Eastern Africa to the World Health Organization (WHO) in the period January 1–December 6, 1977. Since October 16, 1975 — more than 2 years ago — when a case occurred in Bangladesh, smallpox has been detected only in Ethiopia, Kenya, and Somalia, 3 countries which together with Djibouti are linked by the Ogaden Desert to form one epidemiologic unit.

To date, the last known case of smallpox occurred in Somalia on October 26 in the Merca District. The source of this case was a known outbreak in the nearby district of Kurtuware. All 211 contacts were traced, revaccinated, and kept under surveillance. There have been no secondary cases. As of December 6, there were 6 pending outbreaks* in Somalia — the one in Merca and 5 in Bardere.

During October and November surveillance in Somalia has been severely hampered by heavy rains that have made it difficult or impossible to travel by vehicle. Since work has had to be continued on foot, there have been some delays in reporting and incomplete search coverage in certain areas. To combat this, personnel have been concentrated in those areas considered to be at highest risk of having undetected foci or where information is most limited. Currently there are 1,670 national staff and 24 WHO epidemiologists involved in the program. Increased mobility with restoration of complete active searches will be necessary to ensure that all foci have been detected. Accordingly, intensified activities are planned during the dry season, January through April 1978.

The last known case of smallpox in Ethiopia occurred on August 9, 1976, in El Kere Region. In Kenya, the last case was on February 5, 1977, in the Mandera District.

Reported by the World Health Organization in the Weekly Epidemiological Record 52:389-391, 1977

*An outbreak is defined as one or more cases; a pending outbreak is one in which 6 weeks has not elapsed since the onset of rash of the last case.

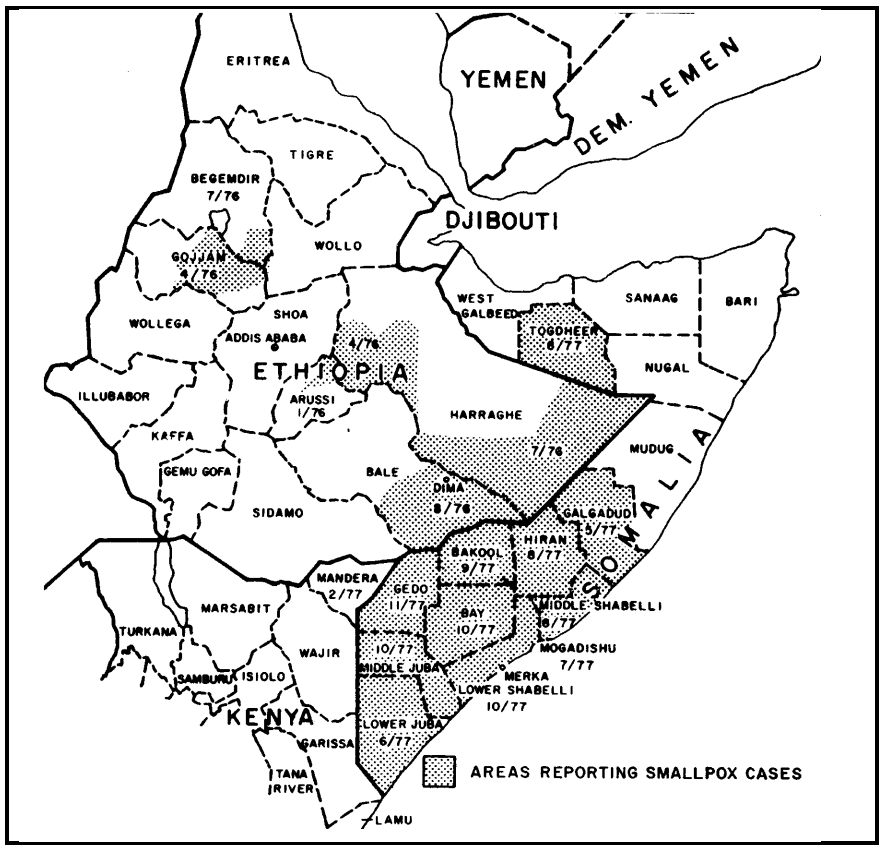
Smallpox Surveillance — Worldwide

MMWR 1978;27:133 (May 5, 1978)

As of April 14, 1978, no cases of smallpox have been reported to the World Health Organization (WHO) from anywhere in the world since the last case had onset of rash on October 26, 1977, in Merka town, Somalia. However, a total of 2 years of effective surveillance must elapse before this last endemic area can be confirmed to be smallpox-free.

Worldwide, since January 1, 1976, smallpox cases have been detected only in certain areas of Ethiopia, Kenya, and Somalia (Figure 1). One year and 9 months has elapsed since cases were detected in Ethiopia; 1 year and 1 month has elapsed since

FIGURE 1. Eastern Africa: The world's last known smallpox foci by area and dates of last cases, as of April 14, 1978



5 cases were detected in Kenya after an importation from Somalia; and 6 months has passed since the last case was found in Somalia.

With the apparent interruption of transmission of the disease on a global basis, smallpox activities are being directed toward promptly certifying and providing authoritative endorsement of this historic event. In January 1978 the Executive Board of WHO endorsed the recommendations of a consultant group on worldwide certification of smallpox eradication which met in October 1977. Recognizing that this certification is based on verifying that 2 years has elapsed with no case of smallpox being detected by a surveillance system which would have detected any case had it occurred, the recommendations called for the establishment of a Global Commission. This independent group of experts is to monitor and review the following steps to be undertaken in 1978 and 1979: (1) certification by international commissions in the 15 countries not yet visited by commissions; (2) special documentation or visits to be required for 16 countries; (3) the request for statements from other countries declaring their smallpox-free status.

If no more cases of smallpox are detected, the countries of Somalia, Ethiopia, Djibouti, Kenya, Yemen, and Democratic Yemen will be eligible for certification in Octo-

ber 1979. These will be the last of the 15 countries to be certified by an international commission, and priority attention is being given to surveillance in these areas.

Reported by the World Health Organization in the Weekly Epidemiological Record 53:97-99, 108, 1978.

Editorial Note—1997

William F Foege, MD, Rollins School of Public Health, Emory University, and former Director, CDC. Walter R Dowdle, PhD, Director of Programs, Task Force on Child Survival and Development, and former Deputy Director, CDC.

Some things need be done only once in the entire history of the world. The development of smallpox vaccine and the eradication of smallpox disease are on the list. Perspective is elusive, even when one contemplates 20 years without a single case of smallpox in the world. Part of the reason is that we all begin our reading "in the middle of the book." Although the full story that went before can never be known, smallpox eradication became possible, and then inevitable, when Edward Jenner, using his clinical powers of observation over a 25-year period during the 18th century, became convinced that an infection with cowpox could protect against smallpox. He then took the next step, inducing immunity by transferring cowpox from the hand of Sarah Nelmes to the arm of James Phipps—creating a tool that would change the health of entire populations (*1*).

In a real sense, the history of modern public health started on that day, May 14, 1796. Word spread quickly, despite communication barriers. By 1806, Jefferson was able to visualize the last case of the disease when he wrote to Jenner, "future generations will know by history only that this loathsome disease has existed" (*1*).

It is a sad commentary that it took 170 years to finally organize to accomplish Jefferson's vision. But when it happened, it brought out the best in science and public health. The resolution at the World Health Assembly in 1965 was unanimous and led to excellent cooperation between the United States and the Soviet Union, even in the midst of Cold War politics. The value of WHO, which represented the health needs of every person in the world, was demonstrated. Workers and resources from around the world were organized for use in the areas of greatest need. The public health situation, rather than political concerns, dictated how the program was to be executed. The United States can be proud of its role in this exciting program, contributing hundreds of workers and millions of dollars for the eradication of a disease that no longer involved our nation.

Twenty years have passed since the last naturally acquired case of smallpox occurred, as reported in the January 6 and May 5, 1978, issues of *MMWR*. Smallpox has not re-emerged from an unrecognized human or animal reservoir, from a variolator's store of infected scabs, or infected cadaver, either unearthed or thawed. There continues to be no evidence to support the theory of a "niche" for human pathogens that, when vacated, will be filled by another. Although speculation increased when monkeypox was recognized as causing human disease, fears decreased when monkeypox was shown to have a low secondary attack rate among unvaccinated humans (*2*). In addition, monkeypox virus, probably arising from a squirrel reservoir, is not ancestral to smallpox virus based on genomic studies (*3*).

The issue of monkeypox again emerged with outbreaks in 1996 (*4*) and 1997 (*5*) in the eastern Democratic Republic of the Congo with speculation about the need for smallpox vaccine to provide cross-protection for the populations at highest risks. Such recommendations must be considered carefully because of the adverse risks of the vaccine, particularly in persons who may be immunocompromised by human immunodeficiency virus infection (*5*). A better understanding of the current epidemiology/epizoology of monkeypox is needed.

Smallpox has been eradicated, but the etiologic agent is not extinct. The virus continues to exist in freezers in secure facilities at one institution in the United States and another in the Russian Federation. During the past 10 years, various individuals and three WHO committees have recommended destruction of virus stocks on the grounds that the world needs to be assured that smallpox will never again be a threat to humankind. In opposition to virus destruction are equally strong views that laboratory stocks serve as a counterbalance to terrorism and a source of unknown future benefits to humankind. In May 1996, the World Health Assembly recommended, subject to further review, that all stocks be destroyed in June 1999.

The legacy of the smallpox program, beyond eradication, has been enduring and includes the Expanded Program on Immunization (with its remarkable reductions of measles and other vaccine-preventable illnesses), the impending eradication of Guinea worm disease and poliomyelitis, and improved global disease surveillance and public health logistics systems. The growing interest in eradication as a global health strategy led to the creation of the International Task Force for Disease Eradication, which reviewed >80 potential candidate diseases and concluded in 1993 that six were eradicable (*6*). The science of infectious diseases eradication was the subject of a multidisciplinary Dahlem Workshop in Berlin in March 1997. As a follow-up to the Dahlem Workshop, a conference is scheduled in Atlanta in early 1998 on Global Disease Elimination/Eradication as Public Health Strategies; this conference will explore the potential synergistic relations between disease elimination/eradication and primary health-care programs throughout the world.

The health benefits of smallpox eradication have been enormous and the economic benefits satisfying. Because of smallpox eradication, the United States saves more each year than its annual dues to WHO. For the first time, social justice in public health has been achieved, with everyone benefiting from a body of scientific knowledge and experience. The benefits will continue to be enjoyed by every person who will ever be born. "Future generations will know by history only" that world cooperation reached an unprecedented level in the 20th century, making this bequest possible.

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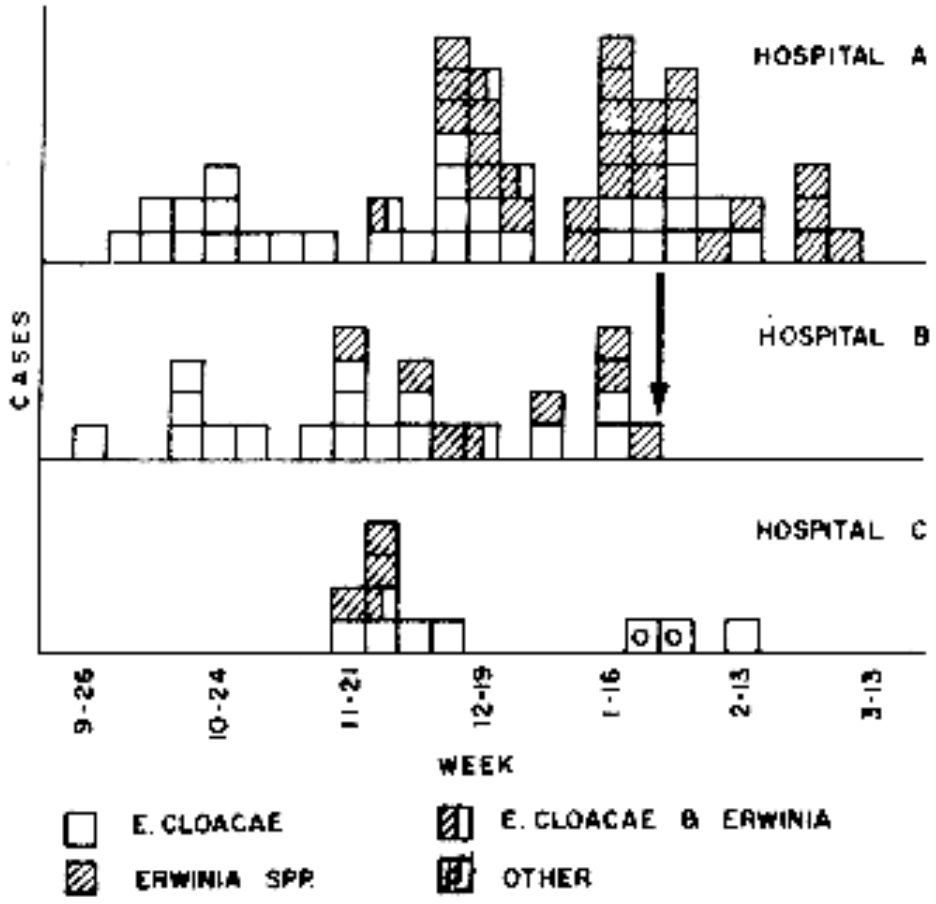
Nosocomial Bacteremias Associated with Intravenous Fluid Therapy — USA

MMWR 1971;20 (Special Supplement) (March 6, 1971)

Between October 1970 and March 1, 1971, eight United States Hospitals in seven states experienced 150 bacteremias caused by *Enterobacter cloacae* or Gram-negative organisms of the Erwinia group. There were nine deaths; all were associated with intravenous (IV) fluid therapy. The Enterobacter bacteremias in all hospitals were substantially increased as compared to previous time periods. Four hospitals which isolated and identified Erwinia had not previously encountered infections with these organisms. In-depth epidemiologic investigations were performed in three of the hospitals (Figure 1).

All eight hospitals utilize fluids and systems manufactured by Abbott Laboratories, which produces approximately 45 percent of all IV fluids sold within the United States. In approximately 30 cases, the same organisms were isolated from blood cultures and contaminated in-use IV fluids. In hospital B (see arrow, Figure 1) no further cases were observed after discontinuance of Abbott products.

Figure 1
IV-ASSOCIATED SEPTICEMIAS, BY WEEK OF ONSET, 1970-1971



Enterobacter cloacae is occasionally encountered as an agent of bacteremia in American hospitals. However, unless fully speciated, this organism will not be identified. Erwinia, most well known as a plant pathogen, has only very rarely been isolated from human infection *(1)*. Erwinia may be confused with members of the Klebsiella-Enterobacter group, and a rather detailed series of biochemical tests, with special emphasis on decarboxylase reactions, are needed to reliably differentiate the organisms.

These septicemias were constantly characterized by intermittent high fever, although shock was infrequent. Young individuals or other patients without predisposing host factors were frequently afflicted. The great majority of cases simultaneously manifested extensive phlebitis at the site of infusion which occurred even when polyethylene catheters had been in place for only brief periods, and also occurred where only scalp vein needles were used. Discontinuance of IV therapy has resulted in dramatic clinical improvement; if such therapy is continued, however, antimicrobials have frequently been without apparent effect on the course of the infection.

Studies of IV systems by CDC have shown a minimum of 6 percent prevalence of contamination within the tubing or bottles after the system has been in use. A significantly greater risk of contamination was noted in all systems where administration apparatus remained unchanged for greater than 48 hours. The studies also revealed that routine once-daily complete change of all IV administration apparatus, especially at the time of replacement of infusion devices (polyethylene catheters, needles, etc.) can greatly decrease the hazard of extrinsic contamination by preventing introduced organisms from propagating to dangerous levels.

Bacterial contamination of the outer surface of the insert discs (synthetic cap liner) of unopened Abbott bottles has recently been demonstrated by CDC, which ranges from 0 to 52 percent among sampled lots. Bacillis species, *S. epidermidis*, *Pseudomonas maltophillia* and yeasts have been most frequently isolated, however, *E. cloacae* or Erwinia species have been isolated from 12 of 212 caps tested. Between April and September 1970, Abbott Laboratories partially converted to a new type of cap liner.

Direct sampling of fluids from intact non-manipulated bottles by CDC has been negative, but transfer of organisms from contaminated caps to the fluid has been effected approximately 25 percent of the time by sequentially striking the cap several times, unscrewing and replacing it, and then hanging the bottle inverted for 24 to 48 hours. Transfer of organisms from contaminated caps to the fluid of bottles, where the cap has not been manipulated, has not been demonstrated, but is currently under further investigation. Once inoculated into commercial dextrose containing solutions, organisms of the Klebsiella-enterobacter group are capable of proliferating at room temperature, whereas other tested members of the Enterobacteriacae or Staphylococci either fail to grow or die.

(Reported by the Food and Drug Administration and the Center for Disease Control.)

Reference:

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Editorial Comment:

The following press release was issued March 13, 1971:

The Commissioner of Food and Drugs, Dr. Charles C. Edwards, and the Director of the Center for Disease Control, Dr. David J. Sencer, today announced that special pre-

cautions must be taken in hospitals, nursing homes, and other health care facilities to reduce the risk of septicemia from the use of Abbott Laboratories intravenous (IV) infusion products. While contamination resulting in septicemia can occur in the use of infusion products from any manufacturer, recent Abbott production appears to present a unique problem. These products will be replaced as rapidly as possible by Abbott, however, these solutions are essential for patient care and cannot be withdrawn before replacement is in hand.

A rising incidence of septicemia caused by organisms rarely associated with septicemia has been found in connection with the use of intravenous fluids in eight hospitals surveyed by the CDC. All eight were users of the Abbott infusion system. CDC has been closely examining the fluids, the infusion apparatus, and clinical reports of septicemia. The plastic liners in some Abbott bottle caps have been found contaminated by the implicated organisms. A tentative conclusion is that the organisms can enter the fluid from the plastic cap liners when the caps are opened and replaced while the bottle is held for later use. There is no evidence that the closure system allows or contributes to contamination before it is opened. It has been shown that when the cap has been removed and replaced that migration of bacterial organism from the cap lining may occur.

The bottles of fluid known to be involved have been manufactured from February 1970 and they bear codes beginning with 842 through 855.

Teams of experts from CDC, FDA, and Abbott Labs are reviewing all aspects of the problem. This review will be completed within a few days and it is expected that a resolution will be developed rapidly.

Meanwhile, with cooperation of the American Hospital Association, hospitals and other users of these solutions are being advised of special procedures to reduce the contamination hazard to a minimum. These procedures include: opening the containers at the point of use only; not replacing the cap; and using the contents of the containers immediately upon opening. Hospitals also are being advised to change IV apparatus at least every 24 hours. The CDC studies have demonstrated that any brand of IV apparatus is more likely to cause infection if left in place longer.

CDC and FDA conclude that the joint actions being taken are reasonable and necessary in the interest of patient care and to prevent a disruption in the availability of these essential drugs.

On the basis of the studies conducted thus far, several additional specific measures which might minimize the risk of contamination from Abbott products are recommended:

1. At the first suspicion of clinical septicemia or fever which might be associated with contaminated intravenous fluid, all existent IV apparatus should be removed and microbiologically sampled; if continued IV therapy is necessary, it should be reinitiated with entirely new equipment and solutions.
2. Bottle caps should not be struck or otherwise traumatized to effect removal. If a cap is not easily removed, the bottle should be discarded.
3. A cap should never be replaced after the bottle has been opened.

Editorial Note—1997

Frank S Rhame, MD, Abbott Northwestern Hospital, Minneapolis; Dennis G Maki, MD, Professor of Medicine, University of Wisconsin, Madison; former EIS officers in the Hospital Infections Section, Bacterial Diseases Branch, CDC, John V Bennett, MD, former Director, Division of Bacterial Diseases, CDC; and William R Jarvis, MD, Acting Director, Hospital Infections Program, National Center for Infectious Diseases, CDC.

In December 1970, CDC's Hospital Infections Section, Bacterial Diseases Branch, first received reports of episodes of nosocomial *Enterobacter* sp. bloodstream infection (BSI). There was early concern about an association with receipt of intravenous (IV) fluids because the patients had no primary infections or cultures yielding *Enterobacter*. Initially, it was hypothesized that this was caused by the vulnerability of IV solution bottle screw-cap closures to extrinsic contamination. By January 1971, several hospitals across the United States reported patients with BSIs caused by *E. cloacae* and an organism then uncharacterized as a human pathogen, *E. agglomerans*. Furthermore, many of the episodes occurred in patients more healthy than those who ordinarily were at risk for nosocomial BSIs, and all of the hospitals used IV fluids manufactured by one company, Abbott Laboratories, Inc. On-site epidemiologic investigations were initiated at two hospitals by Epidemic Intelligence Service (EIS) officers from CDC's Hospital Infection Section. The investigations could not relate the IV-associated BSIs at these hospitals to a particular additive or to any IV system component and could not identify any defect in IV system management leading to extrinsic contamination.

In general, contamination outbreaks involve a single organism; in these investigations, two bacterial species were involved. Nevertheless, the finding of these same two unusual organisms causing BSIs at multiple hospitals decreased the likelihood of extrinsic contamination and raised the possibility of a common source. By February 1971, epidemic organisms were found in the caps of IV solution bottles. Opened and unopened bottles of IV solution were obtained, and cultures of these IV fluid bottles were initiated at CDC. In vitro studies documented that simple, commonly performed manipulations, such as unscrewing the cap, adding a medication, replacing the cap, and inverting the bottle for mixing would transfer the contaminating organisms from the cap to the fluid. After the warning published in *MMWR* on March 6, 1971, CDC and Food and Drug Administration (FDA) teams conducted investigations at both of the Abbott manufacturing plants (*1*). Ultimately, CDC isolated the epidemic strains directly from the solutions in 13 (0.7%) of 1825 1-liter bottles (*2*).

By March 1971, *E. cloacae* and *E. agglomerans* BSIs had been reported from eight hospitals across the United States. Approximately 20 persons at CDC were involved in assembling data from these hospitals, culturing IV bottles and working with Abbott and FDA on the appropriate response to the situation. The bases for action were the occurrence of unexpected primary nosocomial BSIs in multiple hospitals exclusively among patients receiving Abbott IV solutions, the recovery of epidemic organism from bottle caps and several hanging IV bottles, and the termination of an outbreak in a hospital after changing from Abbott IV fluids. Meetings in Washington, D.C., led to the decision to issue the joint press release on March 13 by Charles Edwards, M.D., Commissioner of Food and Drugs, and David Sencer, M.D., Director of CDC. The need for an *MMWR* special supplement, without precedent for this publication, arose be-

cause the *MMWR* dated March 13 had been finalized by Wednesday, March 11. The decision to issue the press release was not made until Thursday and the data underlying it could not have been added to the *MMWR* dated March 13.

The March 13 governmental action was not a total recall of all Abbott IV fluids because it was not clear that there was sufficient substitute IV solution from alternate manufacturers to meet the nation's needs. To reduce the risk for BSI, instructions on proper IV bottle manipulation were issued to minimize transfer of organisms from the cap to the fluid. On March 22, FDA issued a recall of all Abbott IV fluids when it became clear that the scope of the epidemic was larger than initially recognized, that some hospitals continued to have episodes of BSI despite implementation of the March 13 recommendations, and that sufficient substitute IV fluids were available (*3*). By March 31, a total of 405 patients with BSI had been reported, of whom none had had onset after the March 22 recall (*1*). The full epidemiologic analysis published in 1976 (*4*) was delayed in part because of medicolegal considerations, and underscored the exceptional magnitude of the outbreak: estimates of the magnitude ranged from 2000 to 8000 episodes of BSI caused by these contaminated IV fluids. Approximately 10% of the case-patients in the studied hospitals died while bacteremic or soon thereafter.

The cause of this outbreak was ultimately attributed to unexpected consequences of a new cap design for IV solution bottles (*1*). After the March 13 warning, it was learned that the company had been phasing in a new cap type since approximately March 1970, although substantial production did not occur until about November 1970. The old cap liner incorporated a natural red rubber disc between the metal cap and a thin Gilsonite® wafer that was pressed against the bottle orifice by the natural rubber. Fortuitously, the rubber had antibacterial properties against *E. agglomerans* and *E. cloacae*, two organisms unusual among bacteria in their ability to proliferate in acidic, nitrogen-poor, dextrose-containing fluids (*5*). In vitro studies showed that these organisms were drawn up into the cap as cooling occurred after autoclaving but were not destroyed by the new elastomer lined cap. Manufacturing plant environmental cultures documented that these organisms were abundant in the manufacturing plant environment because of spillage of glucose-containing solution that favored their growth. It is uncertain whether the organisms may have been drawn into the fluid itself during cooling or whether it was impossible to remove the caps without transferring organism to the fluid. Furthermore, the United States Pharmacopeia (USP) sampling procedures did not require identification of contaminating organisms, and the required two-step sampling scheme was too insensitive—missing 98% of lots contaminated at a 1% rate. Identification of recovered organisms would probably have revealed the problem earlier.

Surveillance of nosocomial infections had begun at CDC in 1965 when the Hospital Infection Section initiated the Comprehensive Hospital Infections Program (CHIP) study in six community hospitals. CHIP produced high-quality data on infection rates in hospitalized patients and was used to develop nosocomial infection surveillance methods applicable to U.S. community hospitals. In May 1969, CDC initiated the National Nosocomial Infections Surveillance (NNIS) system, a substantially larger program that accepted data from up to 80 hospitals nationwide. These efforts helped establish nosocomial infection surveillance programs in U.S. hospitals. Without such programs, the detection of this outbreak would have been more difficult, and the outbreak likely would have resulted in additional deaths. While several hospitals recog-

nized the phenomenon independently because of clustering of BSIs and/or by the involvement of the unusual organisms, most involved hospitals had small numbers of infected patients and recognized their involvement only in retrospect (*6*).

This outbreak required a compilation of national prospective data to detect, investigate, and terminate. The epidemiologic expertise and laboratory resources required to carry out multiple onsite investigations and in vitro microbiologic studies in a timely fashion were only available at CDC, a national public health institution. During February–April 1971, approximately 3000 cultures of large volume parenteral fluids were performed by CDC laboratory personnel—the extraordinarily large number of cultures resulted in a national shortage of brain heart infusion broth. The necessary and synergistic interaction between epidemiologists and microbiologists in solving the outbreak is still recognized by the prestigious Mackel Award, offered annually to EIS officers in honor of the competence and dedication of the late Donald C. Mackel, who directed the laboratory studies. This outbreak also resulted in development of more sensitive and restrictive USP requirements for monitoring contamination of large volume parenterals by manufacturers and the development of the first guidelines by CDC on the prevention of nosocomial infection (*7,8*). These guidelines were the precursors to the current Hospital Infections Program Nosocomial Infection Prevention Guidelines.

One consequence of this outbreak was the media attention and litigation incurred by some of the involved hospitals. Ironically, it was the active surveillance for nosocomial infections at these hospitals and the quality of their infection-control programs that facilitated recognition of this outbreak. Headlines about BSIs in hospitalized patients were not mitigated by the hospitals' ultimate medicolegal exoneration. The manufacturer incurred considerable economic consequence from this outbreak, even though this outbreak occurred before the era of cooperation between plaintiff's attorneys in product liability suits. The trials were conducted in 1976, and most of the epidemiologic evidence was not admitted. Judgments turned on whether an individual lot could be demonstrated to be contaminated and whether the patient could be proven to have received fluid from that lot. Since lot numbers were not often recorded, few plaintiffs prevailed.

One of the special features of the CDC in response to this crisis was the compression of hierarchy, including the open information channels throughout CDC. For example, during the most intense period of the investigation, the CDC Director was in frequent direct conversation with front-line EIS officers. In negotiating sessions with FDA in Washington, data presentations were made by EIS officers.

This large nationwide outbreak of nosocomial BSIs traced to intrinsic contamination of IV solutions led to widespread changes at industry, hospital, state, and federal levels. Expansion of nosocomial infection surveillance and control programs occurred at the hospital and federal level. There was enhancement of FDA and CDC surveillance for outbreaks attributable to potentially contaminated products, expansion of training programs for infection-control professionals and hospital epidemiologists, development of guidelines for the prevention of nosocomial infection, strengthening of CDC core epidemiologic and laboratory capacity to respond to nationwide outbreaks, and strengthening of FDA and USP requirements for monitoring potential product contamination. Since the institution of these measures, no large nationwide

outbreak of BSIs traced to intrinsically contaminated IV solutions has occurred in the United States.

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Respiratory Infection — Pennsylvania

MMWR 1976;25:244 (August 5, 1976)

A total of 152 persons associated with a state American Legion convention in Philadelphia July 21–24 have been hospitalized with respiratory infections. Onsets of illness were in the period July 22–August 3; the majority occurred from July 25 to July 31. Twenty-two of these patients have died. The deaths, reported over the past week, were primarily due to pneumonia.

Although information about the disease and its epidemiology is incomplete, it appears to be characterized by the acute onset of fever, chills, headache, and malaise, followed by a dry cough and myalgia. Some of the most seriously ill developed high fever and died in shock with extensive pneumonia. No etiologic agent has yet been incriminated. There is no information available concerning other Legionnaires who may be ill with less severe symptoms.

The patients, among several thousand attending the convention, stayed in at least 3 or 4 hotels while in Philadelphia. There is no evidence of increase in respiratory disease in Philadelphia residents, nor has there been any confirmed secondary spread to family members or other contacts. There have been several reports of similar disease in non-conventioneers who were in Philadelphia at the same time as the convention.

Reported by RG Sharrar, MD, City of Philadelphia Dept of Public Health; WE Parkin, DVM, Acting State Epidemiologist, Pennsylvania State Dept of Health; the Bur of Epidemiology and the Bur of Laboratories, CDC.

Follow-up on Respiratory Illness — Philadelphia

MMWR 1977;26:9–11 (January 18, 1977)

Last summer an outbreak of severe respiratory illness occurred in Pennsylvania chiefly among those who had attended a state American Legion convention in Philadelphia July 21–24, 1976 (MMWR 25 [30,33,34]). An estimated 180 cases including 29 deaths occurred (MMWR 25 [38]). An organism has now been isolated in yolk sacs of embryonated hens' eggs that appears to be the etiologic agent. For the purpose of this report the yolk sac isolate is being called a bacterium on the basis of its size and morphology.

The bacterium was first isolated from the lung tissues of 1 fatal case of Philadelphia respiratory disease and 1 fatal case of Broad Street pneumonia (see below) by inoculation of guinea pigs intraperitoneally. After a 1- to 2-day incubation period the guinea pigs developed a febrile illness that was characterized in most animals by watery eyes and prostration. Spleen suspensions of febrile guinea pigs were inoculated into yolk sacs of embryonated eggs from antibiotic-free chicken flocks. The embryos died after 4–6 days, and Gimenez-stained smears of the yolk sacs were found by microscopic examination to contain many bacilli. The bacilli were gram-negative and moderately pleomorphic. Surviving guinea pigs were shown by indirect immunofluorescence to have developed antibody to the yolk sac isolates. Because most bacteria when inoculated into the yolk sac kill the eggs in 1–2 days, an unusual rickettsia was suspected.

The organism is bigger than a rickettsia, however, and the convalescent guinea pig sera failed to react in the complement fixation test with standard rickettsial antigens prepared from *Coxiella burnetii*, *Rickettsia rickettsii*, *R. prowazekii*, and *R. typhi*. Cultivation on sheep blood agar and Trypticase Soy Agar has been attempted at each yolk sac passage. Frequently, no growth has been observed, but yolk sacs infected with 1 isolate have sometimes given many minute colonies after 2–3 days' incubation. The slowness of growth has delayed bacteriological identification.

Evidence for the etiologic role of the yolk sac isolate in the epidemic has been obtained by indirect fluorescent antibody stains carried out by methods that are the same as those in regular use in the diagnosis of rickettsial diseases, except that the microdrops fixed to the slide were prepared from yolk sacs infected with isolate 1 and isolate 2 of the Philadelphia agent. The results in Tables 1 and 2 were obtained with sera from 33 patients who were selected because they were Legionnaire delegates who were hospitalized, survived, and had radiologic evidence of pneumonia and fevers of at least 102 F; they thus represented the most typical survivors.

Table 1 shows some representative results. The sera with high titers gave bright staining at low dilutions which gradually decreased with increasing dilution. The brightness of staining and height of the titers are similar to that observed in other infectious diseases, for example, Rocky Mountain spotted fever. Patients 1, 2, and 3 had distinct increases in antibody titers, and 4 had only a 4-fold increase. The first specimen from patient 5 was already at a titer of 128, and there was no further increase between the eighth and twenty-ninth day of illness.

Table 2 summarizes the results with sera of the 33 Legionnaire patients tested to date; 29 gave results that suggest they were infected with the organism. Seroconversions were seen in 25 patients and antibody rises of more than 4-fold in 19. The maximum titers observed were 128 or greater in 26 out of 29 patients. The titers were usually low in the first week of illness, but they rose rapidly in the second and third weeks. The fact that 3 patients had no serologic response is not surprising since the cases were defined on a clinical and epidemiological basis. The staining of isolates 1 and 2 has been very similar with these sera and with the other sera reported below. Thus the 2 yolk-sac isolates are antigenically very similar if not identical.

Cases of Broad Street pneumonia represent disease clinically similar to Philadelphia respiratory disease that occurred in persons who did not attend the Convention, were within 1 block of Hotel A between July 1–August 18, but said they did not go into Hotel A during the epidemic period. Sera from 4 of the 38 such patients have been tested. Two have shown serologic conversions from titers of 16 or less to 512 or greater. Two had unchanging titers of 32 or less.

As controls for the fluorescent antibody tests, sera were tested from 40 patients unrelated to the outbreak whose specimens had been submitted for rickettsial diagnosis (Table 3). The rickettsial complement fixation tests had failed to demonstrate rickettsial antibody. The sera were first screened at a dilution of 1:32 and those with staining at this dilution were retested at dilutions of 1:16 through 1:512. Most of the titers observed with the yolk sac isolate were low. Two specimens had titers of 64, that is, they overlapped with the lowest titers observed in Legionnaire patients in Table 2. The staining at low dilutions with these sera was only 1+ bright; however, in all the seropositive Legionnaire patients in Table 2 and in the 2 Broad Street pneumonia patients who converted, fluorescence was 3–4+ bright in low dilutions.

TABLE 1. Results with indirect fluorescent antibody stains of the agent cultivated in yolk sacs. Sera from selected patients with Philadelphia respiratory disease.

Patient	Specimen	Day of Disease	16[a]	32	64	128	256	512	Titer	Interpretation[b]
1	S1	1	1+/1+[c]	±/±	0/0	0/0	0/0	0/0	16/16[d]	
	S2	22	3+/3+	3+/3+	2+/3+	1+/2+	±/1+	0/0	128/256	C
2	S1	4	±/±	0/0	0/0	0/0	0/0	0/0	<16/<16	
	S2	11	2+/3+	2+/2+	1+/2+	1+/1+	±/±	0/0	128/128	
	S3	25	3+/3+	2+/2+	2+/2+	1+/1+	±/1+	±/±	128/256	C
3	S1	24	±/±	±/±	0/0	0/0	0/0	0/0	<16/<16	
	S2	34	3+/3+	3+/3+	2+/3+	2+/3+	1+/2+	1+/1+	>512/>512	C
4	S2	12	3+/3+	2+/2+	1+/1+	±/±	0/0	0/0	64/64	
	S3	33	3+/3+	2+/2+	1+/2+	1+/1+	±/1+	0/0	128/256	C
5	S1	8	2+/2+	2+/2+	1+/1+	1+/1+	±/±	0/0	128/128	
	S3	29	3+/3+	3+/3+	2+/3+	2+/±	±/0	0/0	128/64	P
6	S1	5	0/0	0/0	0/0	0/0	0/0	0/0	<16/<16	
	S3	29	0/0	0/0	0/0	0/0	0/0	0/0	<16/<16	N

[a] The reciprocal of the dilution is shown in this and other tables.

[b] C = seroconversion or increase in titer of at least 4-fold with 1 or both antigens. P = classified as positive because the titer was high but showed little change. N = classified as negative because all specimens had low titers.

[c] Brightness of staining: 0 = no staining, ± = questionable staining, 1+ = barely detectable but definite staining, 2+ and 3+ = increasing brightness. The 2 numbers refer to staining of the bacteria in yolk sacs infected with the first 2 isolates.

[d] Highest dilution with definite staining with either antigen.

TABLE 2. Results with indirect fluorescent antibody stains of the agent cultivated in yolk sacs: Summary of results with patients with Philadelphia respiratory disease

Interpretation of Titers		Number of Patients
Seroconversions: >4-fold		19
4-fold		5
Positive (≥64) without seroconversion		5
Negative		4
Maximum titer observed with seroconversions and positives	8192	1
	2048	1
	1024	3
	>512	3
	512	6
	256	6
	128	6
	64	3
Negatives	<64	4
Total patients tested		33

In the outbreak, illness in conventioneers was associated with time spent in Hotel A. The incidence was directly related to time spent in the lobby. Sera were available from some hotel employees of 2 categories: those who worked in the lobby and those who worked in locations removed from the lobby (Table 4). Also shown in the table are the results with sera from a group of Pennsylvania Legionnaires who did not attend the convention. One positive titer in a hotel employee was seen, a cashier checker, who had a titer of 256. The titers with the other employees and the Legionnaires who did not attend the convention were within the range of the 40 non-epidemic sera reported in Table 3.

In 1966 an outbreak of acute pneumonia occurred at a large psychiatric hospital in the District of Columbia. There were 94 cases and 16 deaths. Acute and convalescent sera were available from 14 patients; they were also tested against the antigens from Isolate 1 and 2. Thirteen had distinct rises in titer of 8-fold or more, and 12 had titers of 128 or more. The brightness of staining and titers were the same as those seen with the Legionnaire patients.

The intensity of public interest in the Philadelphia epidemic makes it necessary to provide a factual account of these findings now. The etiology of the outbreak has been unknown. The present findings provide very strong evidence that the 2 epidemics were caused by the bacterium isolated in yolk sacs and that nearly all the cases had the same cause. The bacterium can be identified now by the characteristic disease it produces in guinea pigs, the characteristic death pattern in eggs, the at best dysgonic growth on the bacterial media tried, and by the fluorescent antibody staining results. Other, more complex explanations are possible. For example, the bacterium might be thought of as a secondary invader associated with a virus, but extensive virological searches have failed to reveal a virus and the serologic responses for the bacterium have been present in a very high percentage of the cases. There has not been time to

TABLE 3. Results with sera from control patients clinically suspected to have Rickettsia infections

Titer	Number of Persons
64	2
32	6
16	3
<32	28
<16	1
TOTAL	40

TABLE 4. Serologic results with other persons who did not meet clinical criteria for a case of Philadelphia respiratory disease[a]

	Titers						
	<16	16	32	64	128	256	Total
Hotel employee, lobby		1	2				3
Hotel employee, non-lobby	6	4	2			1	13
Legionnaire, not at convention	3	5	1	2			11

[a] In all these sera the staining, even at low dilutions, was not more than 1+ (barely detectable).

identify the organism taxonomically. The source of the organism in the outbreak is not known, but the search should now be greatly facilitated.

Reported by the Leprosy and Rickettsia Br, Virology Div, Bur of Laboratories, CDC.

Follow-up Survey Data: In December 1976, selected survivors of Philadelphia respiratory disease and matched controls were interviewed concerning smoking habits, liquor and snack food preference, and knowledge of homemade liquor. The 56 patients selected for interview represented all hospitalized male survivors who had been delegates to the American Legion convention and were known to have developed an illness characterized by temperature of 102 F or higher and pneumonia proved by X-ray. The 56 controls were male delegates matched by age who had indicated on earlier survey that they had not been ill since the convention. The interviews were completed with 52 case-control pairs. Cigarette smoking habits at the time of the convention were the only significant associations with illness. The relative risk of illness among cigarette smokers was 3.4 compared to non-smokers ($X^2(1) = 5.5$, $p < .05$, McNemar) (Table 5). Cases also smoked more cigarettes and were more likely to have smoked sample cigarettes available at the convention. A previous survey showed no single cigarette brand common among cases. Pipe or cigar smoking was not associated with illness.

Reported by RG Sharrar, MD, City of Philadelphia Dept of Public Health; E Streiff, RN, MPH, Allegheny County Dept of Health; WE Parkin, DVM, Acting State Epidemiologist, Pennsylvania State Dept of Health; Bur of Epidemiology and Bur of Laboratories, CDC.

TABLE 5. History of cigarette smoking at the American Legion Convention, Philadelphia, July 1976 among case-control pairs

	Cases		
Controls	Smoker	Non-smoker	Total
Smoker	14	5	19
Non-smoker	17	16	33
Total	31	21	52

Editorial Note—1997

David J Sencer, MD, former Director, CDC; Joseph E McDade, PhD, Associate Director for Laboratory Science, National Center for Infectious Diseases, CDC.

A bacterial etiology was not initially evident during the field investigation phase of the Legionnaires disease outbreak. Chest radiographs of case-patients revealed an interstitial pneumonia, which at that time was considered indicative of a viral infection. Because the Legionnaires disease bacterium is refractory to most stains, no bacteria could be visualized when sections of lung tissues from deceased patients were stained by commonly used methods, such as the Brown-Brenn technique. Additionally, no species of bacteria was reproducibly isolated from autopsy materials or clinical specimens because the special nutritional requirements of the Legionnaires disease bacterium precluded its growth on conventional culture media. The bacterium was, however, isolated in guinea pigs and in the yolk sacs of embryonated hens' eggs

and was visualized by Gimenez stain during one of several efforts to isolate Q fever rickettsiae (*Coxiella burnetii*) from specimens of lung tissue collected at autopsy. It subsequently was cultivated on enriched Mueller-Hinton agar using heavily infected yolk sacs as inoculum. The unique nutritional requirements of the bacterium were identified in separate studies, and a new culture medium was developed that now allows routine isolation of the Legionnaires disease bacterium from clinical specimens (*1*).

Determination of the phenotypic and genotypic properties of the Philadelphia isolate indicated that it was a novel species (*Legionella pneumophila*) (*2*). The genus *Legionella* now comprises approximately 40 named species and subspecies that are associated with water. Approximately half of the species have been implicated in human disease; *L. pneumophila* serotype 1, the prototype strain that was isolated following the Philadelphia outbreak, is responsible for most infections.

The epidemic of pneumonia that followed the American Legion convention in August 1976 was one of the most publicized epidemics in which CDC had participated. Daily newspaper reports contained "body counts," rumors of biological and chemical warfare, and accusations of cover-up by CDC. Reports by CDC in the *MMWR*, however, were limited to short back-page accounts, reporting that the epidemic had occurred and was under investigation.

On Friday, January 14, 1977, the director of CDC's Laboratory Division, Charles Shepard, M.D., and microbiologist Joseph E. McDade, Ph.D., went to the office of the CDC Director, David J. Sencer, M.D. After a few hesitant moments, they informed him that they had isolated the agent that had caused the outbreak. Dr. Shepard wanted to take the weekend to redo the isolation in a laboratory where they had not been working to rule out any possibility of contamination.

Although Dr. Shepard did not want to release the information until it was published in the peer-reviewed scientific literature, Dr. Sencer wanted to fulfill CDC's responsibility to immediately release the information to state and local health departments because the outbreak had been in the national news for months and this information could prevent other cases. A solution was found: *MMWR* is a scientific publication, and CDC published and printed *MMWR*. CDC could print a special edition on the following Tuesday, January 18, 1977 (normal publication was on Thursdays). Once it was in print at 1 p.m., it could be given to the news media with an embargo until 3 p.m.

Tuesday morning, as the presses were beginning to run 180,000 copies, Dr. Shepard reported that he had retrieved serum specimens from the serum bank of two earlier unsolved outbreaks of pneumonia, and they were positive for the identical organism. The presses were stopped, and the changes were made.

At 1 p.m., a conference call was scheduled from CDC to the state health officers, the Surgeon General, the National Institutes of Health, and other public health officials participating in the investigation. CDC employees who had worked in any way on Legionnaires disease—from dishwashers in the laboratory to the chiefs of epidemiology and the laboratory—were invited to this conference call. Following that call, CDC conducted a press conference, in which Drs. Shepard and McDade presented the findings and distributed the *MMWR*. This is the only occasion on which an extra issue of the *MMWR* (weekly) has been published.

Legionnaires disease is only one of many new diseases, syndromes, or etiologic agents that have been identified during the past 2 decades (*3*), and CDC has responded to these new challenges. Other noteworthy examples include Lyme disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), toxic-shock syndrome, human ehrlichiosis, hantavirus pulmonary syndrome, hepatitis C virus, and *Escherichia coli* O157. In some instances (for example, HIV/AIDS), both the disease and its etiologic agent previously were unknown to medical science. In others, the disease already existed but was unrecognized. Legionnaires disease apparently occurred sporadically as early as the 1940s. Retrospective analysis of a "rickettsia-like agent," which was isolated from a pneumonia patient in 1947, revealed that this agent was identical to *L. pneumophila* (*4*). However, at the time of its isolation, the source of the bacterium was erroneously attributed to the guinea pigs that were used in the isolation procedure. Since the 1940s, other technologic changes, including the introduction of air-conditioning cooling towers, have facilitated the potential for exposure through dissemination of infectious aerosols of *Legionella* in contaminated water (*5*). This realization has lead to changes in routine maintenance procedures for many aerosol-producing devices such as cooling towers, spas, and respiratory therapy equipment. The development of prevention strategies is an ongoing process involving medical professionals, engineers, and chemical disinfectant manufacturers.

Identification of new etiologic agents undoubtedly will continue. For example, of the approximately 4 million cases of pneumonia that occur in the United States each year, the etiologic agent remains unidentified in up to 50% of cases even when an etiology is actively sought (*6*). Similarly, no etiologic agent is found in 60% of reported foodborne disease outbreaks, most of which are studied using routine diagnostic methods, nor in 32% of diarrheal outbreaks on cruise ships, despite intensive investigation (*7,8*). However, in contrast to the Legionnaires disease investigation, during which the etiologic agent was identified serendipitously, new molecular techniques allow for a more systematic search for infectious etiologies. In particular, the extreme sensitivity of representational difference analysis and consensus sequence-based polymerase chain reaction technology should allow the identification of many etiologic agents that previously have been refractory to culture (*9*).

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Poliomyelitis — United States, Canada

MMWR 1979;28:229–30 (May 25, 1979)

As of May 22, an additional case of polio caused by type 1 poliovirus has been reported in Pennsylvania, bringing to 4 the total number of such cases this year. Two other states have reported suspected cases. Three of the confirmed and both suspected cases are in Amish residents (1,2). In addition, Ontario, Canada, has confirmed a case of paralytic poliomyelitis (type 1 virus) in an Amish woman.

United States: The Pennsylvania Department of Health's most recent report is of a case of non-paralytic polio (aseptic meningitis) in a 36-year-old, non-Amish woman whose vaccination history is unclear. The woman became ill on April 30. She was hospitalized with apparent aseptic meningitis on May 8. The State Laboratory confirmed a poliovirus type 1 isolate from her stool on May 14. The patient is from Mifflin County, where 2 cases of paralytic polio were recently identified in an Amish community (*2*). Although this woman's husband has had regular contact with Amish farmers in the county, the patient, herself, has had no direct contact with this community. She is the first non-Amish ill person identified in 1979 with confirmed poliovirus type 1.

In addition, Iowa and Wisconsin are each currently evaluating a case of acute paralytic illness in a previously unvaccinated Amish person. These 2 patients became ill on April 30 and May 5, respectively. In Wisconsin at least 8 of 20 stool specimens from the patient's unvaccinated family members showed early growth of probable enterovirus.

Canada: Ontario has reported a case of paralytic poliomyeltis in a previously unvaccinated, 25-year-old Amish woman, hospitalized on May 13 with right lower extremity weakness. Her brother was hospitalized the same day with a similar acute paralytic disorder. Poliovirus type 1 has been confirmed from stool specimens of the woman and from her asymptomatic mother and sister. The female patient had attended an Amish wedding in the United States on April 5; Amish persons from various areas, including Pennsylvania, attended the wedding.

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Editorial Note: There have now been 5 confirmed and 3 suspected cases of type 1 polio reported in the United States and Canada in 1979. These cases, from geographically distinct areas, are further evidence of the spread of the type 1—presumably wild-type—poliovirus. The virus appears to have spread from 1 unvaccinated Amish group to another, with transmission enhanced by the extensive travel and large social gatherings characteristic of this population. It is unlikely that the wild poliovirus will spread significantly among the general population, even to areas adjacent to Amish groups, because routine immunization practices have led to a high level of community protection.

Because dissemination of poliovirus is occurring among unvaccinated Amish populations, and because of the possibility for increased (often inapparent) transmission throughout the upcoming summer months, CDC considers the entire American Amish population at risk of infection and recommends vaccination of all unvaccinated Amish persons (including adults) with a full series of trivalent oral poliovirus vaccine

(TOPV). TOPV is also recommended for unimmunized persons who are in daily contact with an unvaccinated community from which a wild-type poliovirus is isolated. Immunization levels of children in areas near Amish communities should be reviewed to assure that routine immunizations are up-to-date.

CDC has notified all 21 states known to have Amish residents of the new cases and of current recommendations. These states include Delaware, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Michigan, Minnesota, Missouri, Montana, New Jersey, New York, Ohio, Oklahoma, Pennsylvania, Tennessee, Virginia, and Wisconsin. Particularly in these states, physicians should include polio in the differential diagnosis of aseptic meningitis and acute paralytic disease.

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Follow-Up on Poliomyelitis — United States, Canada, Netherlands

MMWR 1979;28:345–6 (July 27, 1979)

No new cases of epidemic-associated poliomyelitis have been reported to CDC during the past month. Two cases previously reported as suspected have now been confirmed, bringing the 1979 total of confirmed cases in the United States and Canada to 17. Fourteen of these cases (all paralytic) occurred in unvaccinated Amish persons; 2 (both nonparalytic) were in unvaccinated non-Amish persons, who lived in or near an Amish area; and 1 case (paralytic) occurred in an Amish infant, who received oral poliovirus vaccine 5 days before becoming ill. In the latter case, the patient had laboratory evidence of recent infection with both type 1 and type 2 poliovirus; the other 16 cases were clearly due to a wild (type 1) poliovirus. These 17 cases have been reported from 4 different states (Pennsylvania, 8 cases; Iowa, 3; Wisconsin, 3; Missouri, 1) and Canada (2). Immunization campaigns for the Amish are continuing; at least half of the nation's Amish have now received 1 or more doses of oral poliovirus vaccine.

Antigenic marker tests, consisting of (a) the van Wezel Method, using cross-absorbed rabbit antisera against vaccine and nonvaccine (wild) poliovirus strains and (b) the modified Wecker method, using guinea pig antisera against vaccine strains, have been performed on the poliovirus type 1 strains isolated from 5 U.S. cases and from a household contact of a sixth case. All isolates were nonvaccine-like in their antigenic characteristics.

The type 1 poliovirus isolated from the first 1979 poliomyelitis patient (an Amish female from Pennsylvania) shows a resemblance to a wild type 1 strain isolated in Kuwait in 1977 (*1*). Type 1 strains from cases occurring in the 1978 epidemic in the Netherlands and Canada also showed a resemblance to the Kuwait poliovirus strain (*1*).

Epidemiologic information also links last year's poliomyelitis epidemic in the Netherlands and Canada with this year's outbreak in the United States and Canada. During the 1978 outbreak, members of the affected religious group traveled from the Netherlands to Canada, where cases subsequently appeared. An Amish family from an Ontario town 15 miles from the affected area moved in late summer 1978 to the Pennsylvania town where the first U.S. Amish case subsequently occurred, in January

1979. There were also other, less well-defined contacts between Amish persons in Ontario and Pennsylvania.

Reported by Dr. A. van Wezel and Dr. van Zermarel, Rijks Institute voor der Volksgezondheit, the Netherlands; S Acres, MD, Dept of National Health and Welfare, Ottawa; State Epidemiologists from Iowa, Missouri, Pennsylvania, and Wisconsin; Virology Div, Bur of Laboratories, and Viral Diseases Div, Bur of Epidemiology, CDC.

Editorial Note: Both laboratory and epidemiologic information have suggested a link between the poliovirus type 1 strain from the 1979 outbreak in the United States and Canada with the type 1 strain responsible for last year's outbreak in the Netherlands and Canada. The onset of illness in the last case occurring in Canada in 1978 was in August, more than 4 months before the onset of illness in the first 1979 case, which occurred in Pennsylvana. Nearly 3 months elapsed before the next 1979 cases occurred, and these were also in Pennsylvania. These data suggest that the wild poliovirus circulated inapparently through several generations without causing paralytic disease. The absence of new cases of paralytic poliomyelitis reflects, in part, the success of the multi-state immunization campaigns for the Amish; the possibility of new cases remains, because the wild type 1 poliovirus may continue to be excreted by some infected persons throughout the summer months. However, the risk of additional cases is diminishing as more of the susceptible Amish persons receive vaccine.

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Editorial Note—1997

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MMWR should never again publish an article describing a contemporaneous outbreak of polio in the United States. Although it was not known at the time the 1979 *MMWR* articles were published, these articles describe the last outbreak of polio in the United States. The 1979 outbreak occurred in unvaccinated Amish persons living in Iowa, Missouri, Pennsylvania, and Wisconsin. Overall, 15 cases of illness caused by wild poliovirus type 1 occurred among U.S. citizens: all 10 paralytic cases occurred among unvaccinated Amish persons; three cases of transient paralysis occurred among unvaccinated Amish persons; and two nonparalytic cases occurred among unvaccinated members of the Mennonite church who were in frequent contact with Amish persons. Epidemiologic and virologic evidence indicated this outbreak resulted from importation of poliovirus from the Netherlands through Canada (Ontario), where outbreaks had occurred during 1978 in members of religious groups with objections to vaccination. Intensive studies in an outbreak-affected area where there were extensive contacts between Amish and non-Amish persons indicated that existing immunity levels provided an effective barrier to extensive circulation of poliovirus in the general community.

Investigation and control of the outbreak involved exceptional cooperation between local and state officials in the 21 states with Amish populations and CDC. As highlighted in the May 25, 1979, *MMWR* article, CDC considered the entire U.S. Amish population to be at risk for polio and recommended vaccination of all Amish persons,

including adults. Epidemiologic aspects of the investigation were coordinated by CDC Epidemic Intelligence Service officers Marjorie Pollack, M.D., and Melinda Moore, M.D., under the supervision of Larry Schonberger, M.D., of CDC's Division of Viral Diseases (which then was responsible for polio surveillance). The programmatic efforts to reach and vaccinate Amish populations were coordinated through the Division of Immunization and state immunization programs, and used the efforts of many CDC public health advisors. Vaccination efforts involved extensive contacts with Amish groups in the 21 states and ultimately resulted in vaccination of approximately one half of Amish persons in the United States.

Another notable feature of this outbreak was the very close collaboration between epidemiologists and the laboratory. Using oligonucleotide mapping (the newest tool available at the time), CDC laboratory scientists Milford Hatch, Ph.D., and Olen Kew, Ph.D., were able to show that the virus responsible for illness in the United States was identical to the virus that had caused outbreaks in the Netherlands and Ontario, Canada. Subsequent development of more sophisticated techniques such as genomic sequencing further confirmed the link. This was one of the first instances of use of "molecular epidemiology" at CDC and heralded a collaboration between epidemiologists and laboratorians that has been a hallmark of the global polio-eradication program.

The 1979 outbreak demonstrated both the tremendous progress to date in achieving protection of the U.S. population but also the fact that polio could find a way to reach the remaining pockets of susceptible persons in the country. In addition, the outbreak made clear the necessity of taking a global approach to polio.

During the first half of the 20th century, paralytic polio was a major cause of illness and public concern in the United States; reported cases increased annually and peaked at approximately 20,000 reported cases in 1952. The introduction of inactivated poliovirus vaccine (IPV) in 1955 and the subsequent introduction of oral poliovirus vaccine (OPV) in 1961 had a dramatic impact on the occurrence of disease, with the numbers of reported cases and outbreaks progressively decreasing to very low levels by 1970.

Throughout the 1970s, there was continued evidence of possible circulation of wild poliovirus in the United States. During the decade, 17 cases of polio were imported from other countries and for 30 cases of paralytic polio, no foreign source could be determined (endemic cases). Since the reports in 1979, no endemic cases have been reported in the United States, although imported cases (on average less than one per year, predominantly from Mexico) continued to occur throughout the 1980s.

In 1985, the Health Ministers of the Americas adopted a goal of regional eradication of polio from the Western Hemisphere by 1990. The subsequent implementation of polio-eradication strategies (focusing on routine vaccination with OPV, mass vaccination of all children aged 0–4 years through annual National Immunization Days [NIDs], effective surveillance, and response to cases) resulted in a dramatic reduction in importations of polio. The last case of paralysis caused by indigenously acquired wild poliovirus in the Americas had onset in August 1991, and in 1994, the hemisphere was certified free of polio by an independent commission.

Other industrialized countries have had experiences similar to those of the United States. Most western European countries have been free of epidemic or endemic polio for many years, although limited outbreaks occurred in Finland in 1984–1985 and in

the Netherlands in 1992–1993. Asia and Africa have been the areas most affected by polio in recent years.

In 1988, the World Health Assembly adopted a goal of global eradication of polio by 2000, and eradication efforts began throughout the world, largely using the strategies developed in the Americas. Under World Health Organization (WHO) leadership, a remarkable partnership of public and private organizations has been formed. Chief among these has been Rotary International, United Nations Children's Fund (UNICEF), and CDC. Additional financial support has been provided by the governments of Australia, Canada, Denmark, Italy, Japan, Norway, Sweden, the United Kingdom, and the United States. In the private sector, most notable has been the extraordinary commitment of Rotary International, which is donating approximately $400 million to support the effort and is providing essential financial and physical support from local Rotarians, including volunteers for social mobilization, vaccination posts, and advocacy efforts. A global laboratory network has been developed by WHO to support the eradication effort.

Unprecedented public health efforts by many countries where polio is endemic have characterized the polio-eradication effort. In several countries (including Afghanistan, El Salvador, and Sudan), civil wars have been temporarily suspended to allow vaccination of children in both government- and rebel-controlled areas. Seventeen nations in the Middle East, the Caucasus, and Central Asia have cooperated in coordinating NIDs (Operation MECACAR). Probably the most spectacular accomplishment has been the administration of OPV to more than 257 million children aged <5 years in a single week in 1996 as a result of simultaneous efforts in Bhutan, China, India, Myanmar, Nepal, Pakistan, Thailand, and Vietnam.

The reported incidence of polio in India has declined dramatically. China, with approximately one fourth of the world's population, has not detected indigenous wild poliovirus since 1994. The only indigenous transmission of polio in 1997 in WHO's Western Pacific Region occurred in the area of the Mekong delta. In the face of financial and societal crises, 31 countries in Africa have conducted NIDs, and those that have not done so already are in the planning phases.

The remaining challenges in the fight against polio are 1) resources to fully implement eradication strategies (a shortfall of approximately $50 million per year in donor support still remains); 2) maintenance of the political will to see the program through to ultimate success; and 3) development of surveillance systems in many countries to assure that circulation of poliovirus (or its absence) can be detected.

The United States has much to be proud of in the fight against polio. The U.S. Congress has supported global polio-eradication efforts through both the Agency for International Development and CDC. In addition, the United States is, and will continue to be, one of the major beneficiaries of polio eradication. The polio-free status the United States has enjoyed since 1979 comes at a cost, both personal and financial. Each year in the United States, there are five to 10 cases of vaccine-associated polio, a personal and societal tragedy; this number should be reduced substantially as a result of the recently adopted sequential IPV-OPV schedule. An estimated $230 million also is spent each year to maintain the high levels of polio vaccine coverage. Once polio is eradicated from the planet, polio vaccination can be discontinued, and the respective resources can be devoted to other important global health problems. In 1987, the objective of eradication was underscored: "Global eradication of poliomye-

litis is inevitable; the only question is whether we will accomplish it or pass on the needed action to our successors. We believe we should act now to leave the legacy of a poliomyelitis-free world for our children" (*1*). It now seems clear that this commitment will be fulfilled.

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Toxic-Shock Syndrome — United States

MMWR 1980;29:229–30 (May 23, 1980)

Cases of a newly recognized illness known as toxic-shock syndrome (*1*) have recently been reported to CDC by state health departments in Wisconsin, Minnesota, Illinois, Utah, and Idaho. Physicians in 8 other states have reported individual cases to CDC or to investigators at the University of Colorado, Denver.

Toxic-shock syndrome typically begins suddenly with high fever, vomiting, and profuse watery diarrhea, sometimes accompanied by sore throat, headache, and myalgias. The disease progresses to hypotensive shock within 48 hours, and the patient develops a diffuse, macular, erythematous rash with non-purulent conjunctivitis. Urine output is often decreased, and patients may be disoriented or combative. The adult respiratory distress syndrome or cardiac dysfunction may also be seen.

Laboratory studies reveal elevated blood urea nitrogen, serum creatinine, bilirubin, and creatine phosphokinase levels, and white blood cell counts with marked left shifts. Platelet counts are low in the first week of illness but are usually high in the second week.

Patients require large volumes of fluid to maintain perfusion and usually require intensive care. In the recovery phase, there is desquamation of at least the palms, soles, or digits and often of other skin areas as well.

Since October 1, 1979, 55 cases have been reported to CDC. Fifty-two of these (95%) have been in women. The mean age is 24.8 years, with a range of 13-52 years. Seven deaths have occurred, for a case-fatality ratio of 13%.

Of 40 patients in whom a menstrual history was obtained, 38 (95%) had onset of illness with the 5-day period following onset of menses. Two others had onset of illness 10 days after onset of menses. Moreover, 13 patients have had recurrence of symptoms with a subsequent menstrual period.

In 33 of 45 (73%) patients cultured, *Staphylococcus aureus* was isolated from the throat, cervix, vagina, or rectum. Four of 15 patients (27%) tested for *Herpesvirus hominis* had serologic or cultural evidence of herpes infection. No evidence for leptospirosis, Rocky Mountain spotted fever, viral exanthematous diseases, or streptococcal scarlet fever has been found in those patients in whom it has been looked for.

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Editorial Note: Toxic-shock syndrome is a serious disease of unknown etiology. It affects primarily young women of child-bearing age who have been previously healthy, and it has a case-fatality ratio for reported cases of 10%-15%. This ratio is probably high because severe cases are easier to recognize. In Wisconsin, where surveillance has been very active, the case-fatality ratio has been 3.2%. The incidence of

the disease is not known but is apparently low. The increasing number of reported cases over the past 6 months is probably due to increasing recognition. In support of this theory, a review of medical charts in Wisconsin for the past 2 years revealed 6 cases fitting the case description that had not previously been recognized as toxic-shock syndrome.

The syndrome resembles Kawasaki disease (mucocutaneous lymph node syndrome) in several respects, namely fever, rash with subsequent desquamation, and cardiac involvement. However, shock, which is prominent in toxic-shock syndrome, is not usually seen in Kawasaki disease. The character of the rash is also different in the 2 diseases: it is a maculopapular one in Kawasaki disease but a non-papular, diffuse erythroderma in toxic-shock syndrome. Azotemia and thrombocytopenia are rarely seen in Kawasaki disease and are common in toxic-shock syndrome. Kawasaki disease classically occurs in children less than 5 years of age; some recently reported cases of "adult Kawasaki disease" (*2,3*) may actually be cases of toxic-shock syndrome.

Toxic-shock syndrome was first recognized in 7 children aged 8-17 years, 3 of whom were boys (*1*). In 5 of the 7, *S. aureus* was isolated from the nasopharynx, vagina, or localized abscess. At that time it was hypothesized that the syndrome was caused by a toxin elaborated by the staphylococci. Although *S. aureus* was isolated from vaginal cultures in two-thirds of patients in the current report, no control study has been done to show that this prevalence is unusually high. The isolation of *Herpesvirus* in a small number of cases probably reflects stress-related recurrence of infection and not an etiologic role for the virus. CDC, in cooperation with a number of investigators, is setting up a nationwide case-control study to try to define the epidemiologic features and the cause of this disease.

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Editorial Note—1997

Arthur L Reingold, MD, University of California, Berkeley. Gene W Matthews, JD, Legal Advisor to CDC. Claire V Broome, MD, Deputy Director, CDC.

Although case reports of "Staphylococcal scarlet fever" had been published in the medical literature as far back as the 1920s, a 1978 report describing seven cases of what was named toxic-shock syndrome (TSS) heralded the apparent emergence of TSS in late 1979 and early 1980 (*1*). The report about TSS in the May 23, 1980, *MMWR* and the veritable landslide of studies of TSS that followed demonstrate the speed and effectiveness with which astute clinicians—together with public health officials, epidemiologists, and laboratory scientists—can respond to an "emerging" infectious disease threat. Did TSS truly "emerge" at that time, or did the intensive case-finding efforts of clinicians and epidemiologists in states such as Wisconsin and Minnesota simply make it appear to "emerge"? The limited data available from retrospective

chart-review studies that were designed to identify TSS cases, whether previously diagnosed or not, clearly demonstrated that the number of cases of TSS in women of reproductive age increased beginning in the late 1970s (*2–4*). Cases of TSS in men also occurred during that time but at a low and stable rate. Thus, what "emerged" during late 1979–early 1980 was not all TSS, but TSS in reproductive-aged women, particularly menstruating women, as reflected in the dramatic data presented in the *MMWR* report—of the 55 reported cases, 95% occurred among women, and 95% of the cases among women for whom information was available had onset of their illness within the 5-day period following onset of menses.

The startling proportion of TSS cases identified during 1979–1980 among women who had onset during menstruation led investigators to focus on understanding the risk factors for development of menstrual TSS, rather than TSS in general. The wave of rapidly completed case-control studies of menstrual TSS that followed clearly demonstrated that use of various brands and styles of tampons was by far the most important risk factor for TSS during menstruation (*5–8*). Although the relative importance of absorbency, chemical composition, and other tampon-related factors in determining the risk for menstrual TSS has remained difficult to determine, the most plausible explanation for the "emergence" of menstrual TSS in the late 1970s was the manufacture and widespread use of more absorbent tampons made of a variety of materials not previously used in tampons. There is no evidence to suggest that changes in *Staphylococcus aureus*, the source of the toxin that causes TSS, were responsible for the emergence of menstrual TSS.

The week after the *MMWR* report appeared in May 1980, Dr. William Foege, the director of CDC at the time, testified before the Senate Subcommittee on Health regarding "toxic dumps." Given the widespread news media attention the *MMWR* report had received and a perceived connection between toxic dumps and toxic-shock syndrome, Dr. Foege also was asked about TSS at that hearing, and he optimistically promised "an answer" by the end of 1980. Although much more was learned about TSS during the years that followed (e.g., the biologically important properties of TSS toxin-I, the toxin responsible for most cases of TSS, particularly menstrual cases), in retrospect Dr. Foege was correct. From the public health point of view, before the end of 1980, enough was known about menstrual TSS based primarily on observational epidemiologic studies to promulgate recommendations (*9,10*) that led to a substantial reduction in the risk for menstrual TSS.

Perhaps less well known in the public health community is the important legal precedent that emerged from the civil litigation surrounding menstrual TSS. Faced with a large number of lawsuits filed by women with menstrual TSS, one of the tampon manufacturers filed suit to compel CDC to release the names and other personal identifiers of all women who had participated in the CDC case-control studies of menstrual TSS. Because the results of these studies (and hence the "collective evidence" of the study participants) were being introduced as evidence by women in their lawsuits against the manufacturer, the manufacturer argued that it had a fundamental legal right to know who these women were and even cross-examine them. Although the manufacturer had been given copies of all the data tapes and all the raw data forms from the studies (with identifiers removed) so its experts could reanalyze the results, the manufacturer also argued that it needed to re-interview the study participants several years after the case-control studies had been conducted to assess the

extent to which bias had been introduced at the time of the original interviews (*11*). The federal appeals court decided that the manufacturer could not have access to the personal identifiers of the study participants. The court ruled that in furtherance of its mission to protect the public health, CDC must be able to "conduct probing scientific and social research supported by a population willing to submit to indepth questioning." The court further ruled that "disclosure of the names and addresses of … research participants could seriously damage this voluntary reporting" and that "even without an express guarantee of confidentiality there is still an expectation, not unjustified, that when highly personal and potentially embarrassing information is given for the sake of medical research, it will remain private" (*12*). Thus, the series of events that unfolded following the publication of the *MMWR* report not only led to an expeditious public health response to the emergence of menstrual TSS but to enhanced legal protection at the federal level of the public health research process.

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Reye Syndrome — Ohio, Michigan

MMWR 1980;29:532,537–9 (November 7, 1980)

In addition to a previously reported study from Arizona (*1*), CDC has received reports of studies conducted in Ohio and Michigan which suggest a relationship between Reye syndrome and salicylates (i.e., aspirin) taken during an associated antecedent illness.

Between December 1978 and March 1980, a prospective case-control study of Reye syndrome was conducted by the Ohio State Department of Health. This study involved 6 pediatric centers in the state and examined the possible relationship between Reye syndrome and medications taken during the antecedent illness. One hundred fifty-nine cases were identified in this study; slightly more than half were relatively mild, developing only stage I encephalopathy (difficult to arouse, lethargic, sleepy). A large percentage of these patients were identified during an outbreak of influenza A (H1N1) that occurred in December 1978-March 1979 and an outbreak of influenza B that occurred in December 1979-March 1980, or had varicella as an antecedent illness.

Reye syndrome patients and controls, selected from the same school classroom or neighborhood and matched for age, sex, race, and the occurrence of a similar antecedent illness (respiratory, varicella, or gastrointestinal) within 1 week of that which occurred in the case, were interviewed concerning medications taken between the time of onset of the antecedent illness and either admission to the hospital for Reye syndrome (for cases) or recovery from the illness (for controls). For each Reye syndrome case, the date of onset of vomiting, which is usually associated with the onset of Reye syndrome, was recorded. The frequency of usage of only 2 medications was found to be significantly different statistically in cases and controls. Salicylates, including those contained in various compounds, were the only medications which were taken significantly more frequently in cases (95/98, 97%) than controls (114/160, 71%) ($p<.001$). All of the Reye syndrome cases with a history of salicylate ingestion took salicylates during their antecedent illness and prior to the onset of the preencephalopathic vomiting associated with this syndrome. Multiple logistic analysis using a model that included histories of salicylate ingestion, fever, headache, and sore throat has demonstrated that although a history of fever was significantly greater in cases than controls, this difference did not account for the even stronger association of cases with a history of salicylate ingestion. Using this model, the estimated relative risk of Reye syndrome for patients taking salicylates was 11.3 (95% confidence limits 2.7-47.5). Histories of headache and sore throats were not significantly different in cases and controls. Medications containing acetaminophen were taken by only 16% (16/98) of cases compared to 32% (51/160) of controls ($p<0.01$). Although analysis has not yet been completed concerning the dose of salicylates ingested by the patients with Reye syndrome, the majority had a history of taking no more than normally recommended. The medication history was usually obtained from parents within 7-10 days (for cases) and 10-20 days (for controls) after the onset of antecedent illness.

The recently reported study from Michigan involved 25 patients with Reye syndrome and 44 controls selected in a manner similar to that of the Ohio study, matched for the same criteria, and interviewed 4 to 83 days (mean 6.5 weeks) after their acute illness. When cases and controls were retrospectively matched for fever ($\pm 1^{o}$ F), aspi-

rin was taken significantly more often in cases (14/14, 100%) than controls (14/21, 67%, p<0.02), and acetaminophen-containing compounds were taken significantly less often in cases (0/14), than in controls (6/21, 29%, p<.05).

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Editorial Note: Although the epidemiologic association between Reye syndrome and antecedent viral illnesses is well established, the etiology of this rare disease remains unclear. Several previous reports have suggested the possibility that medications taken during the antecedent illness of patients with Reye syndrome may play a role in the development of this disease, and aspirin is 1 medication which has been mentioned frequently (*2-4*).

The Ohio and Michigan studies reported here and the previously reported smaller study from Arizona (involving 7 cases and 16 controls) are the only controlled studies of the relationship between Reye syndrome and medications taken during the antecedent illness reported since this disease was first described. All 3 of these studies involved in-home interviews focusing specifically on medication histories of Reye syndrome patients and controls.

A number of potential problems are encountered when conducting and analyzing such studies. These include 1) difficulties in obtaining comparable and accurate medication histories in patients following a significant event (Reye syndrome) when compared to controls who have had a relatively minor illness, and the difficulty of accurate recall of events several weeks later, 2) the possibility that cases had a more severe antecedent illness and/or a pre-encephalopathic illness that included severe vomiting and headaches—both of which may have predisposed them to take more medications than controls—and 3) the presumed need to select cases and controls with the same viral infections, including influenza B, influenza A (H1N1), and varicella, since Reye syndrome is thought to be more strongly associated with these infections.

It is possible that parents of patients with Reye syndrome were more likely than parents of controls to recall events immediately preceding their child's major illness and hospitalization, including medications taken by their child during this period. Recall of medication histories for Reye syndrome patients may also have been more accurate and complete than the recall for controls because parents of cases were frequently interviewed earlier after their child's acute illness than were parents of controls. However, the fact that only aspirin or salicylate-containing compounds were found to have been taken significantly more frequently during the antecedent illness in cases than controls in these studies suggests that the association between Reye syndrome and salicylates may indeed be real. Furthermore, the fact that acetaminophen-containing compounds were taken by significantly fewer cases than controls in both studies, which might be expected if Reye syndrome patients were more likely to use salicylates than acetaminophen for fever or other symptoms, suggests that the recall of parents of cases was not greater than the recall of parents of controls for these medications.

Another possible reason for differences in medication histories in cases and controls is that Reye syndrome patients may have a more severe or prolonged antecedent illness and/or may subsequently develop a pre-encephalopathic illness, associated

with severe vomiting, for which they might receive additional medications. Because elevated temperatures are 1 major reason for taking salicylates, both of these studies have attempted to compare the effects of differing histories of fever among cases and controls. In the Michigan study, even when cases and controls were matched for degree of fever, the difference in salicylate usage remained significant. Analyses completed in the Ohio study have demonstrated that a history of fever, as well as headaches and sore throats—symptoms which might also cause cases to take more salicylates than controls—did not account for the observed differences in salicylate ingestion. Additional analyses in Ohio of aspirin ingestion histories of Reye syndrome patients for the specific period between onset of prodromal illness and onset of vomiting demonstrated that all of 95 patients who received salicylates received some during their antecedent illness—before the onset of pre-encephalopathic vomiting. The possible confounding effects of other symptoms and combinations of symptoms are being further examined in the Ohio study.

Reye syndrome is rare and associated frequently with certain viruses. Thus, comparison of medication histories in cases and controls who had the same viral infection may be important. In both of these studies, controls were selected from the same school and had a prodromal illness within 1 week of that of the cases. It is probable that many cases and controls were matched for infection because a large percentage of the cases occurred during outbreaks of influenza, and varicella patients were matched with other children who had varicella. Further analysis of the salicylate association by specific type of infection should be possible in the Ohio study.

In 1976 the Food and Drug Administration advised that, when treating children who develop vomiting associated with a viral illness, caution should be exercised in using acetaminophen, salicylates, and antiemetics because of the suspicion that these drugs, in combination with a viral illness (a possible cause of vomiting in children) might contribute to the development of Reye syndrome (*5*). The results of these studies suggest that during certain viral illnesses the use of salicylates—even before the onset of vomiting—may be a factor in the pathogenesis of Reye syndrome. In view of these data, parents should be advised to use caution when administering salicylates to treat children with viral illnesses, particularly chickenpox and influenza-like illnesses.

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Editorial Note—1997

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Reye syndrome (RS) was first described in Australia (*1*) and in the United States in 1963 (*2*). During the 1960s and 1970s, RS outbreaks in the United States became in-

creasingly recognized in association with outbreaks of influenza and following chickenpox. National surveillance for RS, first conducted during the 1973–74 nationwide epidemic of influenza B, resulted in the recognition of regional as well as nationwide outbreaks of RS. Although children of all ages were affected, incidence peaked among children aged 5–15 years. During the initial years of national surveillance, 236–555 cases were reported each year; the largest number occurred in association with outbreaks of influenza B and influenza A(H1N1). Population-based studies suggested that the average annual incidence among children aged <18 years was approximately one case per 100,000 persons. Case-fatality rates reported through national surveillance were initially as high as 40% and between 20% and 35% during the late 1970s to mid-1980s.

Although anecdotal reports during the 1970s had suggested the possibility of an association between RS and aspirin, the series of studies reported in 1980—the first from Arizona (involving seven cases and 16 controls) followed by larger studies conducted in Michigan and Ohio—were the first case-control studies to examine this issue. However, the possibility that a commonly used medication such as aspirin, which had been prescribed for several decades for febrile illnesses by those taking care of pediatric patients, might be associated with a severe and frequently fatal illness was not readily accepted by many in the medical community. As a reflection of the controversial nature of this matter, the initial Editorial Note published in the November 7, 1980, issue of *MMWR* outlined several of the most important potential limitations of these studies and the considerations that had led CDC to conclude that the studies were strongly suggestive of an association between aspirin use and increased risk for RS. In an effort to fulfill CDC's public health responsibility, the Editorial Note advised parents to "use caution when administering salicylates to treat children with viral illnesses, particularly chickenpox and influenza-like illnesses."

In October 1982, after CDC received a report of a fourth case-control study conducted in Michigan during the 1980–81 influenza season demonstrating a similar association, CDC convened a working group of expert consultants to review all four studies. The working group, which included pediatricians and epidemiologists as well as representatives of the Food and Drug Administration (FDA) and the American Academy of Pediatrics (AAP), reviewed the studies that had been completed and the many concerns expressed by those in the medical community, including consultants and representatives of the pharmaceutical industry. The working group supported CDC's original recommendation and stated that "until the nature of the association between salicylates and RS is clarified, the use of salicylates should be avoided, when possible, for children with varicella infections and during presumed influenza outbreaks" (*3*).

Soon after CDC made these recommendations, FDA conducted an independent audit and analysis of the data from the Ohio and Michigan studies. FDA then convened a scientific workshop to review the data, including analyses completed by FDA. Experts from the academic community, the pharmaceutical industry, and consumer organizations attended the meeting and had opportunities to present their independent analyses and concerns and to express their opinions regarding the studies. After an intensive review of all the concerns, the scientific working group concluded that the new analysis supported earlier evidence of the association between use of aspirin and increased risk for RS. As a result of this review process, in June 1982, the Surgeon

General issued a recommendation advising "against the use of salicylate and salicylate-containing medications for children with influenza and chickenpox" (*4*).

Despite the numerous reviews by expert panels and intense scrutiny of the first four studies, many continued to express concerns about these studies, including industry representatives, the Office of Management and Budget (*5*), and the executive committee of the AAP, which issued a statement calling for further investigation. These concerns focused on the nature of the case-control studies and the many potential epidemiologic issues in such studies, including potential biases of selection and reporting as well as possible confounding (*5*). As a result of the concerns expressed by many groups, in December 1982, the Assistant Secretary of Health appointed a Public Health Service Task Force, comprised of representatives from CDC, FDA, and the National Institutes of Health, to assist in planning and conducting additional research on this issue. A decision about warning labels on packages of certain medications for children was deferred pending the results of this research (*5*).

The Public Health Service Task Force designed a new epidemiologic study to address the concerns that had been raised about the first four studies. A committee was convened by the Institute of Medicine to serve as an advisory board to review the protocol, monitor the study's progress, and review the analysis and results. Between February and May 1984, a pilot study, designed to test the methods for the main study of the relation between medication use and risk for RS, was undertaken. The pilot study, which involved 14 states and 33 pediatric tertiary-care centers, demonstrated a high odds ratio (16.1; lower 95% confidence limit=4.6) associated with the ingestion of aspirin during an antecedent respiratory or chickenpox illness and the development of Reye syndrome, consistent with the risks observed in previous studies. Evaluation of the epidemiologic issues raised concerning previous studies did not indicate that any of these issues could explain the observed association. Although in 1983 there had been no agreed-upon plans to publish the pilot study, the study was subsequently published in October 1985 (*6*) at the recommendation of the Institute of Medicine committee. In March 1986, FDA ruled that all over-the-counter aspirin and aspirin-containing products were required to be labeled with a warning about RS.*

Following completion of the pilot study, the main study of RS and medications was conducted during January 1985–May 1986. Although 70 pediatric tertiary-care centers throughout the United States participated in this study, including many that had previously reported the largest number of cases through CDC's national surveillance, only 33 cases of RS that met the study criteria were identified during the 17-month study period, which included two influenza seasons. However, the number of cases enrolled was fewer than had been expected based on prior experience and than had been specified by the original protocol (at least 100 cases), and the decision was made to discontinue the study because of the small number of cases identified, which reflected the declining incidence of RS that had been observed nationally during the preceding several years. In addition, in this study, as in the earlier studies, a high odds ratio was observed that could not be explained by any of the epidemiologic issues that the study had sought to address (*7*).

Although several years were required to address all the concerns about the initial studies, assessment of temporal trends in RS in the United States indicate that a dra-

*51 FR 8180–8182

matic decline in the incidence of this disease began to occur in the early 1980s soon after the initial and subsequent *MMWR* reports of these studies. This decline appeared to coincide with a decline in aspirin use among children that occurred as a result of the publicity surrounding these studies (*8–10*). The initial studies conducted during the early 1980s suggested that aspirin was administered to up to 70% of children with febrile respiratory illnesses. The national intervention involving the removal of a risk factor, aspirin use among children, was associated with a marked reduction in the incidence of this disease, providing the most convincing corroborating evidence for the association first reported in the case-control studies.

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Pneumocystis Pneumonia — Los Angeles

MMWR 1981;30:250–2 (June 5, 1981)

In the period October 1980–May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

Patient 5: A previously healthy 36-year-old man with a clinically diagnosed CMV infection in September 1980 was seen in April 1981 because of a 4-month history of fever, dyspnea, and cough. On admission he was found to have *P. carinii* pneumonia, oral candidiasis, and CMV retinitis. A complement-fixation CMV titer in April 1981 was 128. The patient has been treated with 2 short courses of TMP/SMX that have been limited because of a sulfa-induced neutropenia. He is being treated for candidiasis with topical nystatin.

The diagnosis of *Pneumocystis* pneumonia was confirmed for all 5 patients antemortem by closed or open lung biopsy. The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses. The 5 did not have comparable histories of sexually transmitted disease.

*Paired specimens not run in parallel.

Four had serologic evidence of past hepatitis B infection but had no evidence of current hepatitis B surface antigen. Two of the 5 reported having frequent homosexual contacts with various partners. All 5 reported using inhalant drugs, and 1 reported parenteral drug abuse. Three patients had profoundly depressed *in vitro* proliferative responses to mitogens and antigens. Lymphocyte studies were not performed on the other 2 patients.

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Editorial Note: *Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients (*1*). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis* pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of *in vitro* cellular-immune function in otherwise healthy human hosts (*2,3*). Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV anti-body. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection; 40 (21%) of the same group had at least 1 other major concurrent infection (*1*). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) of 190 males reported to be exclusively homosexual had serum antibody to CMV, and 14 (7.4%) had CMV viruria; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viruria (*4*). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than in urine, but also that seminal fluid may be an important vehicle of CMV transmission (*5*).

All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia.

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Editorial Note—1996

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The June 4, 1981, report of five cases of *Pneumocystis carinii* pneumonia (PCP) in homosexual men in Los Angeles was the first published report about acquired immunodeficiency syndrome (AIDS). This report in *MMWR* alerted the medical and public health communities 4 months before the first peer-reviewed article was published (*1*).

The timeliness of this report can be credited to the public health sensitivity of the astute reporting physicians and the diligence of CDC staff. Dr. Gottlieb and his colleagues at the University of California at Los Angeles School of Medicine and Cedars-Mt. Sinai Hospital worked closely with the CDC Epidemic Intelligence Service Officer assigned to the Los Angeles Department of Health Services to summarize the data and draft this brief report. When news of these cases reached CDC, scientists in the Parasitic Diseases Division of CDC's Center for Infectious Diseases already were concerned about other unusual cases of PCP. That division housed the Parasitic Diseases Drug Service and requests for pentamidine isethionate to treat PCP in other similar patients in New York had been called to the attention of these scientists by the CDC employee who administered the distribution of this drug (which was not yet licensed and was available in the United States only from CDC).

In July 1981, following the report of these cases of PCP and cases of other rare life-threatening opportunistic infections and cancers (*2*), CDC formed a Task Force on Kaposi's Sarcoma and Opportunistic Infections. A key first task facing CDC was to develop a case definition for this condition and to conduct surveillance. The CDC case definition was adopted quickly worldwide. Results from active surveillance conducted in the United States rapidly established that the syndrome was new, and the number of cases was increasing rapidly (*3*). By the end of 1982, the distribution pattern of cases strongly suggested that AIDS was caused by an agent transmitted through sexual contact between men (*4,5*) and between men and women (*6,7*) and transmitted through blood among injecting-drug users and among recipients of blood or blood products (*8–10*). Cases also were identified among infants born to women with AIDS or at risk for AIDS (*11*), and the epidemic extended beyond the life-threatening reported cases to include persistent unexplained lymphadenopathy (*12*).

To prevent transmission of AIDS, in 1983 the Public Health Service used epidemiologic information about the condition to recommend that sexual contact be avoided with persons known or suspected to have AIDS and that persons at increased risk for AIDS refrain from donating plasma or blood (*10,13*). In addition, work was intensified toward developing safer blood products for persons with hemophilia. These recommendations were developed and published only 21 months after the first cases were reported and well before the first published reports identifying what is now termed HIV as the etiologic agent of AIDS (*14,15*). Isolation of HIV enabled development of assays to diagnose infections; characterization of the natural history of HIV; further

protection of the blood supply; development of specific antiviral therapies; and expansion of surveillance criteria to include other conditions indicative of severe HIV disease. Research and prevention programs for HIV have contributed greatly to scientific and programmatic approaches to other public health problems.

During 1981–1996, approximately 350 reports related to AIDS were published in *MMWR*, an average of two per month since June 1981. Throughout the HIV epidemic, timely publication of reports about AIDS and related topics in *MMWR* have continued to play a crucial role in alerting health professionals and the public.

In 1996, HIV transmission occurs worldwide and has an impact in all countries (*16*). In the United States, prevention efforts have been successful at reducing HIV transmission. For example, blood-donor deferral and blood screening have virtually eliminated HIV transmission through blood and blood products, and adoption of less risky behaviors has greatly reduced sexual transmission between men; most recently, therapeutic advances have reduced transmission from mother to newborn (*17*). However, in the United States, AIDS has been diagnosed in 548,000 persons, and 343,000 have died. HIV infection has become the leading cause of death for persons aged 25–44 years, and an estimated 650,000–950,000 persons are living with HIV infection. Throughout the world, HIV continues to spread rapidly, especially in impoverished populations in Africa, Asia, and South and Central America. The emergence of the HIV pandemic demonstrates the vulnerability of the world's populations to previously unknown infectious diseases.

The first 15 years in the recorded history of AIDS have included remarkable scientific successes and countless examples of individual courage and accomplishment. Although these accomplishments provide hope for the future, further efforts are needed to halt the steady spread of HIV throughout the world.

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Isolation of *E. coli* O157:H7 from Sporadic Cases of Hemorrhagic Colitis — United States

MMWR 1982;31:580,585 (November 5, 1982)

Since the beginning of August 1982, stool isolates of *Escherichia coli* serotype O157:H7 have been identified at CDC from specimens obtained from four patients in two states. Three of four patients had an unusual bloody diarrheal illness; each illness began suddenly with severe crampy abdominal pain followed within 24 hours by watery diarrhea, which subsequently became markedly bloody. One patient underwent a laparotomy to rule out appendicitis. All patients recovered within 7 days without complications or specific therapy. In one instance, *E. coli* O157:H7 was isolated from the stool of a patient's spouse. This fourth patient had abdominal cramps and non-bloody diarrhea. Since early August, 25 additional sporadic cases of this unusual illness have been reported to CDC, but appropriately collected stool specimens were available in only two of these. *E. coli* O157:H7 was not isolated from either specimen. The four patients with sporadic cases in which *E. coli* was isolated from stools and 24 of the remaining 25 patients with sporadic cases had eaten hamburgers from a variety of sources (including homes and/or local or national-chain restaurants) within the week before they became ill.

Examination of stool samples from sporadic cases of this recently recognized diarrheal illness, currently designated "hemorrhagic colitis," began at CDC after *E. coli* O157:H7 was isolated from patients in two separate outbreaks of this illness earlier this year in Oregon and Michigan. Illness was associated with eating hamburgers at restaurants of one national chain.

Hemorrhagic colitis appears to be a distinct clinical entity, characterized by severe crampy abdominal pain, grossly bloody diarrhea, little or no fever, a characteristic barium-enema finding of marked edema involving the cecum, ascending and/or transverse colon, and the absence of usual pathogens in stool.

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Editorial Note: The diagnoses of hemorrhagic colitis are based on the typical clinical presentation and isolation of *E. coli* O157:H7 from the stool specimens. Early stool collection (within 4 days after onset of illness and before any antibiotic exposure) is crucial for detecting the *E. coli*, so physicians encountering typical cases need to ensure that stool samples are obtained and a portion held frozen (preferably at –70 C [–94 F] or on dry ice) while their laboratories perform routine examinations for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, and parasites. If these test results are negative, arrangements can be made through the state epidemiologist and state laboratory director to look for *E. coli* O157:H7 in the frozen specimen. Those state laboratories that do not have the antisera to identify *E. coli* O157:H7 may wish to send either the whole frozen stool or 10 picks (if possible) of *E. coli* colonies to CDC. This strain of *E. coli* O157:H7 does not ferment sorbitol, and this biochemical property may facilitate screening for this serotype. Further studies are under way at CDC to better

characterize the epidemiology of hemorrhagic colitis, the reservoir of *E. coli* O157:H7, and serologic methods to confirm infection.

Epidemiologic investigation of the outbreaks showed that one source of *E. coli* O157:H7 is hamburger. Other enteric diseases, such as salmonellosis, have been reported following consumption of hamburger (*1*). Careful handling and adequate cooking of raw meat products should minimize or eliminate the risk of contracting infectious diseases from this source.

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Editorial Note—1997

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A journey of a thousand miles must begin with a single step.
—Lao-Tzu, Chinese philosopher

This description of four persons with diarrheal illness attributable to *E. coli* O157:H7 was among the earliest published references to this pathogen and the first report of this problem to be published in *MMWR*. From this modest beginning, *E. coli* O157:H7, the most commonly identified member of a group of organisms that is now referred to as the Shiga toxin-producing *E. coli* (STEC), has become one of the best-known emerging pathogens and one that is considered prototypic for the current paradigm of foodborne diseases in the United States (*1*). Over its 15-year history, *E. coli* O157:H7 has evolved as a major problem for primary-care practitioners, pediatric nephrologists, infectious-disease physicians, public health authorities, and those in the child-care setting and the food industry. In the process, the public health imperative to address this problem has influenced the careers of many of CDC's Epidemic Intelligence Service officers. For example, during a 2-year training assignment to the Washington State Department of Health, this author devoted a substantial amount of time investigating outbreaks attributed to this organism and systematically interviewing the hundreds of persons in that state with sporadic cases of *E. coli* O157:H7 infection (*2*).

As all successful public health practitioners and clinicians quickly learn, there is no better way to develop a feel for a disease and its risk factors than by talking to patients with the illness. In reading the *MMWR* article of 1982, it is striking to discover how many of the now classic features of *E. coli* O157:H7 infection could be identified in those four initial patients—these features are typical of hemorrhagic colitis, including abdominal cramping and nonbloody diarrhea rapidly progressing to bloody diarrhea in the absence of prominent fever. In addition, the report notes the occurrence of nonbloody, culture-confirmed disease; the suggestion of person-to-person transmission (which was subsequently confirmed); the great potential for misdiagnosis and inappropriate clinical procedures (in this case laparotomy); and spontaneous recovery without specific therapy, obviating the need for antimicrobial agents (*3*). The report also highlights another critical issue—the failure to collect appropriate specimens to diagnose this and other enteric pathogens. Even today, with the increasingly high profile of this disease, clinicians often fail to consider the diagnosis of *E. coli* O157:H7 or

to collect appropriate specimens, and laboratories often fail to use necessary screening techniques for its identification.

However, one element of this disease was not mentioned in the 1982 report. None of the four patients developed hemolytic uremic syndrome (HUS) nor was it mentioned as a potential complicating factor. HUS is now recognized to occur in 5%–10% of reported cases of *E. coli* O157:H7; it occurs most commonly in patients with this disease who are aged <5 years (*3*). Remarkably, the outbreaks in Oregon and Michigan early in 1982, which led to the initial identification of *E. coli* O157:H7, are among the only ones recognized in which none of the case-patients developed HUS, probably because few of the illnesses occurred in children (*4*). It was not until the following year that the association between *E. coli* O157:H7 and HUS was first reported (*5,6*). However, two outbreaks of HUS had occurred earlier in North America before this association was recognized, including one in 1980 outside of Toronto in association with apple juice (*7*) and one in 1982 in Sacramento (*8*). The history of this problem highlights the need for rapid reporting and thorough evaluation of clusters of unknown etiology. These two outbreaks probably were due to infections with *E. coli* O157:H7, because in North America, most cases of HUS—the most common cause of acute renal failure of childhood—are associated with this infection (*9*). The combination of the severity of the clinical syndrome, the frequency of severe complications, and the lack of specific therapeutic interventions account for the perception of *E. coli* O157:H7 as one of the most feared emerging pathogens.

The initial outbreaks of *E. coli* O157:H7 were associated with two outlets of the same fast-food chain, and illness was linked to undercooked hamburgers. The *MMWR* report mentioned that most of the persons with sporadic hemorrhagic colitis had eaten hamburgers from a variety of sources. Since this report, many other *E. coli* O157:H7 outbreaks, including a large outbreak in 1993 in the Pacific Northwest (*10*), have been linked to ground beef. Although cattle are known to be a major reservoir for this pathogen, the ecology of the organism in animals is poorly understood.

However, accumulating experience has established a diversity of sources for *E. coli* O157:H7, including apple juice and cider, raw vegetables such as lettuce, raw milk, and processed foods such as salami (*1*). Some recent outbreaks have been related to low-level contamination of widely dispersed products, which are more available as a result of advances in the food production and distribution industry. In such instances, outbreaks are marked by small numbers of cases occurring over wide geographic areas. These outbreaks are difficult to detect and investigate. Expanded use of subtyping methods, such as pulsed-field gel electrophoresis for seemingly sporadic cases of *E. coli* O157:H7, will increase the likelihood of detecting diffuse outbreaks (*11*). Although this will expand knowledge of this pathogen, investigation of such outbreaks is likely to further strain health department resources.

Despite the substantial gains in knowledge about *E. coli* O157:H7 since its recognition 15 years ago, many fundamental questions and concerns remain. For example, the reasons for the original emergence of this pathogen and for its geographic spread are not known. In recent years, the organism has become a global health problem; in 1996 alone, major outbreaks were reported in Germany and Scotland, and the largest recognized outbreak, affecting approximately 5000 persons, occurred in Japan (*12*). How frequent is this infection? In a recent study of 10 hospitals from all U.S. regions, *E. coli* O157:H7 was the second or third most commonly isolated bacterial enteric

pathogen in four hospitals, and its overall isolation rate was more than one third of that for *Shigella* sp. (*13*). However, despite its frequency and the availability of inexpensive commercial tests for screening and identification, by the end of 1994 only approximately 50% of U.S. clinical laboratories were screening either all stools or bloody stools for *E. coli* O157:H7 (*14*). Because misdiagnosis can lead to unnecessary therapies and procedures and because person-to-person spread is not uncommon, stool specimens from all patients with a history of acute bloody diarrhea should be cultured for this pathogen (*13*).

Other issues that need to be addressed include 1) determining the public health importance in North America of other STEC—STEC have been recognized as the cause of two outbreaks in the United States and appear to be more common than *E. coli* O157:H7 in other parts of the world, such as Argentina and Australia; 2) deciding whether laboratory screening approaches in the United States should be changed to identify other STEC; 3) determining why some persons develop HUS after STEC infection and others do not, and whether there is any secondary prevention for this complication; 4) identifying the best primary prevention strategy; and 5) estimating the extent to which measures such as Hazard Analysis Control Critical Point work to reduce the threat of *E. coli* O157:H7 to the food supply, and what other measures might be necessary. Efforts to address these and other questions are included in the President's Food Safety Initiative, which was issued in May 1997 (*15*). Such efforts are critical to enhance understanding of *E. coli* O157:H7, other known foodborne pathogens, and as yet undiscovered pathogens that will constitute the foodborne challenges of the future.

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Original report published with new editorial note in *MMWR* 1997;46:700–4 (August 1, 1997).

NONINFECTIOUS CONDITIONS

Pentachlorophenol Poisoning in Newborn Infants — St. Louis, Missouri, April–August 1967

MMWR 1967;16:334–51 (October 7, 1967)

From April to August 1967, nine cases of a clinically distinct illness characterized by fever and profuse sweating occurred in a small nursery for newborns in St. Louis, Missouri. Two of the cases were fatal. Early in the course of the outbreak the disease was felt to be an intoxication, but the nature of the poison and the mode of exposure of the patients remained obscure. Only after the ninth case developed was it discovered that an antimildew agent, containing a high concentration of sodium pentachlorophenate (the sodium salt of pentachlorophenol), was being used in the hospital laundry. All of the clinical, epidemiological, and biochemical evidence indicated that this outbreak resulted from pentachlorophenol poisoning. The only identified mode of exposure was skin absorption of sodium pentachlorophenate residues on diapers and other fabrics, resulting from the misuse of the antimildew agent in the final laundry rinse.

The outstanding clinical feature of the illness was extreme diaphoresis. Attendants consistently noticed that the infants' clothing and brows were drenched with sweat. Nevertheless, the neonates nursed avidly. As the disease progressed, fever rose as high as 103 F, respiratory rates increased, and breathing became labored, though auscultation of the lungs was normal and cyanosis was absent. Other common findings included tachycardia, hepatomegaly, and irritability followed by lethargy. Anorexia, vomiting, and diarrhea were notably absent. Stiffness of the neck, muscular fasciculations, and convulsions were not observed. Skin rashes or evidences of inflammation or irritation of the skin were not seen.

Laboratory tests frequently showed a progressive metabolic acidosis, proteinuria, a rising blood urea nitrogen, and "pneumonia" or "bronchiolitis" on X-ray. Bacterial and viral cultures of blood, cerebrospinal fluid, nose, throat and stool revealed no pathogens. Autopsy findings of the two fatal cases showed fatty metamorphosis of the liver in both cases and fatty vacuolar changes in the renal tubules of one case.

All except one of the seriously ill infants, a fatal case, were transferred to other hospitals for treatment. After the first fatal case occurred, the attending physicians suspected a toxic cause and therefore promptly performed exchange transfusions on each of the seriously ill infants who were subsequently transferred for medical care. This treatment yielded dramatic results. Within minutes to hours, the infants became more responsive and had less respiratory distress. Fever and sweating disappeared, as did metabolic acidosis. Renal function returned to normal during the next few days. Except for the two fatal cases, recovery was apparently complete.

The first four cases developed between April 17 and 19 among a group of 25 infants who were in the nursery during this interval. The first infant to become ill died. The institution was closed on April 24 and thoroughly cleaned and disinfected before reopening on May 3. A second cluster of four cases occurred between May 10 and 15. One of these also was fatal. The average age of these eight cases, at onset of illness, was 8.9 days. Several additional suspect cases with fever and sweating were detected among 13 infants who had been discharged from the hospital in apparent health between April 17 and May 15.

From the time of the first recognition of the outbreak, an intensive and persistent search was made for toxic substances in the environment of the infants. A solid-stick evaporating deodorizer had been used without change in practice for 4 years. A commercial exterminator had sprayed regularly with a carbamate insecticide monthly for 2 years within the hospital, but never in the nursery. The management of drugs and the preparation of babies' formulas revealed no deviations that were likely to permit the introduction of a toxic substance to this many babies.

For the preceding 10 months, a commercially available disinfectant containing a mixture of synthetic phenolic derivatives had been repeatedly applied to surfaces that came in contact with infants' skin.

One-dimensional thin-layer chromatography of serum specimens obtained from the first eight cases was performed. These tests revealed the presence of a phenolic substance in all test specimens, which was similar to a phenolic ingredient of the disinfectant. This substance was thought to be the toxic chemical causing the disease.

The nursery was closed and recleaned. Use of the suspect disinfectant was abandoned, and all equipment that had been treated with it was discarded or rendered free of phenolic residues by extensive cleaning with alcohol. New linens and diapers were purchased and the nursery reopened July 11.

On August 29, an 8-day-old infant had the acute onset of an illness identical to the previous eight infants. The infant received an exchange transfusion and promptly recovered. A follow-up survey of infants discharged from the hospital in July and August revealed six additional infants who had the characteristic excessive sweating in a milder form of the same syndrome.

The formerly suspect disinfectant was no longer in use. Reinvestigation of laundry procedures disclosed a previously overlooked source of phenols. An antimildew agent, containing 22.9 percent sodium pentachlorophenate and 4.0 percent trichlorocarbanilide, was being used in the terminal rinse of all nursery linens and diapers, despite a warning on the label that the compound "must not be used" in laundering diapers.

This product had been in use in the laundry since March 1966. The recommended quantity was one ounce of powder per laundering cycle, but it was ascertained that the laundry was actually using 3 to 4 ounces.

Thin-layer chromatography of the serum and urine of the new case revealed an abnormal substance with characteristics that were identical to those detected in the previous infants' sera. Further studies in two different laboratories with improved methods of analysis have shown that the chemical in the urine and serum of the new case was pentachlorophenol, and was clearly not one of the phenolic ingredients in the previously suspected disinfectant. Additionally, pentachlorophenol was identified in freshly laundered diapers obtained from the nursery. The quantity of pentachlorophenol varied from 1.5 to 5.7 mg. per diaper. Pentachlorophenol, when fed to rats, was found to be highly toxic and was isolated from urine of surviving rats in concentrations comparable to that found in the sick child. Unfortunately, no samples from the earlier cases remained for these more sophisticated analyses.

Actions have been instituted to prevent further illnesses that might be caused by the misuse of this product, or two other sodium pentachlorophenate-containing products that are recommended for similar purposes. The manufacturer has been directed to trace all sales and shipments of these products during the past 18 months, and to

remove such products from all hospitals and any establishment that is involved in general laundry work. The company has voluntarily ceased sale of these three products.

(Reported by J. Earl Smith, M.D., Health Commissioner, Division of Health, Department of Health and Hospitals, City of St. Louis, Missouri; L.E. Loveless, Ph.D., Chemist, Clinical Laboratories, St. Louis, Missouri; E. A. Belden, M.D., Consultant, Communicable Disease Control, Local Health Services Section, Division of Health, Missouri Department of Public Health and Welfare; the Epidemiology and Pesticides Programs of the National Communicable Disease Center, Atlanta, Georgia; the Toxicology Section, Occupational Health Program, National Center for Urban and Industrial Health, Cincinnati, Ohio; and a team of EIS Officers.)

Editorial Note: The clinical, laboratory, epidemiological, and pathological findings, as well as the prompt response to exchange transfusion, all indicate a toxic, rather than an infectious, cause of this outbreak. The fever, sweating, and acidosis are consistent with intoxication with certain phenolic derivatives, which are known to increase the metabolic rate (*1*). The symptoms described here are remarkably similar to industrial accidental poisonings resulting from overexposure to pentachlorophenol or its sodium salts (*2,3*). The exact manner in which the infants became poisoned cannot be established, but the most reasonable explanation is absorption through the intact skin as a result of repeated contact with diapers, blankets, and linens containing small, but readily absorbable, quantities of sodium pentachlorophenate. The antimildew agent, which is labelled not for use in laundering diapers or hospital linens, nevertheless, was in use in this hospital. Pediatricians, hospital administrators, housekeepers, and local health authorities should check commercial diaper services and hospital laundries to ensure that this product is not in use.

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Editorial Note—1996

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This report, one of the first well-documented accounts of an investigation of a noninfectious disease problem to be published in *MMWR* after responsibility for the publication had been transferred to CDC, illustrates one of the most difficult challenges facing environmental epidemiologists—exposure assessment. Even in acute situations such as that described in this report, the search for a toxic agent and the route of exposure is difficult and time consuming. In investigations of chronic and many environmentally related illnesses, exposures that may have occurred over an extended period may be particularly difficult to characterize accurately; the paucity of accurate exposure data has been termed the "Achilles heel" of environmental epidemiology (*1*).

As illustrated by this investigation in St. Louis in 1967, the use of innovative laboratory methodologies has been critical to improving the accuracy of exposure assessments. For example, during this investigation, epidemiologists initially relied on the

laboratory techniques of thin-layer chromotographic analysis of patient specimens to identify a phenol as the probable etiologic agent; more advanced laboratory methods were used to confirm the causative role of this agent and to further focus the investigation. Since 1967, the close collaboration between epidemiologists and laboratory scientists during environmental investigations has continued to strengthen, and the development of biomarkers of exposure, disease, and susceptibility has been critical in assisting public health scientists in exposure assessment (*2*). Environmental epidemiologists in state and federal health agencies are addressing the difficulties of accurately classifying exposure in other innovative ways. For example, computer mapping techniques, such as Geographic Information Systems, have enabled investigators to more accurately use environmental sampling data to represent individual exposure. Finally, although the investigation in St. Louis was highly focused, the approach to this outbreak underscored the public health benefits of basic "shoe leather epidemiology" for solving problems regardless of their etiology.

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Human Lead Absorption — Texas

MMWR 1973;22:405–7 (December 8, 1973)

In December 1971, the City-County Health Department in El Paso, Texas, discovered that an ore smelter in El Paso was discharging large quantities of lead and other metallic wastes into the air. Between 1969 and 1971, this smelter had released 1,116 tons of lead, 560 tons of zinc, 12 tons of cadmium, and 1.2 tons of arsenic into the atmosphere through its stacks (Table 1).

Twenty-four hour air samples to determine the amounts of lead and other heavy metals suspended in the atmosphere were collected throughout 1971 and again between July 1972 and June 1973 by the local health department. Both series of tests showed that mean concentrations of metallic wastes in the air were highest immediately downwind of the smelter and that levels decreased logarithmically with distance from the smelter. The annual mean lead level immediately downwind of the smelter in 1971 was 92 $\mu G/m^3$ and in 1972-73 was 43 $\mu G/m^3$; the U.S. Environmental Protection Agency's proposed safe upper limit for airborne lead content is 2.0 $\mu G/m^3$ of air *(1)*. No metallic emissions were found near any of 15 other industrial establishments studied in El Paso.

Similarly, soil samples taken by the health department at selected sites within the urban area between June and December 1972 showed the highest concentrations of lead and other metals to be in surface soil from within 0.2 miles of the smelter (Figure 1). Samples of drinking water, milk, and food obtained from homes in El Paso between January and March 1972 by the health department were uniformly free of lead.

Preliminary testing programs to evaluate the effect of the environmental contamination on human blood lead levels were conducted in El Paso between January and March 1972 by the local health department, the smelting company, and CDC. These initial studies showed that 43% of persons in all age groups and 62% of children through age 10 years living within 1 mile of the smelter had blood lead levels $\geq$40 $\mu G\%$, a level considered to be evidence of undue lead absorption *(2)*. There was a lower prevalence among persons living at greater distances from the smelter. No cases of overt lead poisoning were noted.

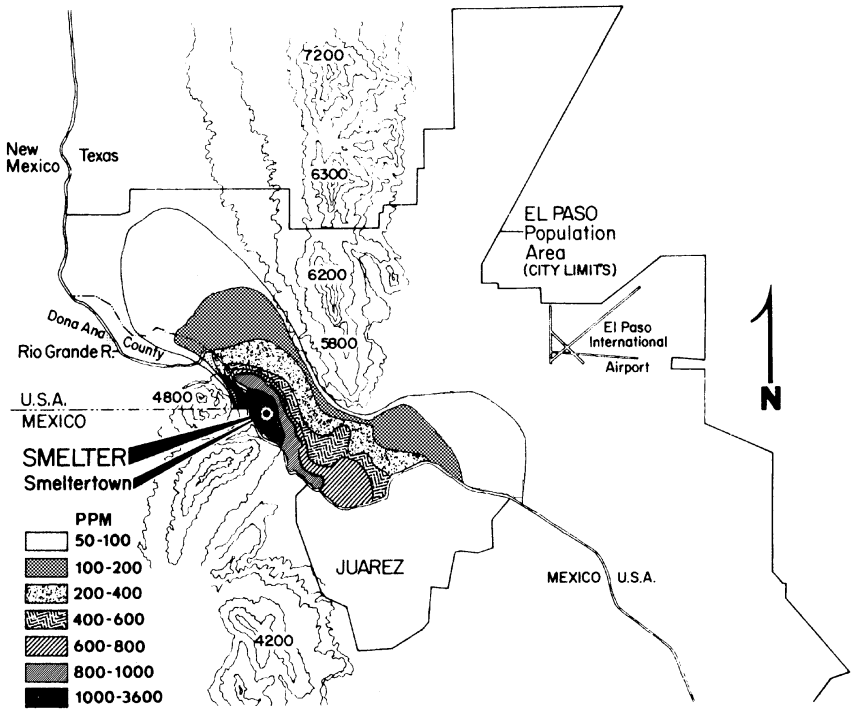
In August 1972, a random survey of the entire population living within 4.1 miles of the smelter in south and west El Paso was conducted by the health department and CDC. The area was divided along census tract lines into 3 strata, roughly concentric

Table 1
Particulate Waste Stack Emissions (in Tons [t]), by Year
El Paso Smelter, 1969–1971

Year	Total Particulates	Lead	Cadmium	Zinc	Arsenic
1969	1,443t	292t	3.3t	139t	0.3t
1970	2,274	511	4.9	264	0.6
1971	1,282	313	3.8	157	0.3
Total	4,999t	1,116t	12.0t	560t	1.2t

Source: El Paso City-County Health Department

Figure 1
LEAD SURFACE SOIL LEVELS
EL PASO, TEXAS, AND DONA ANA COUNTY, NEW MEXICO — 1972

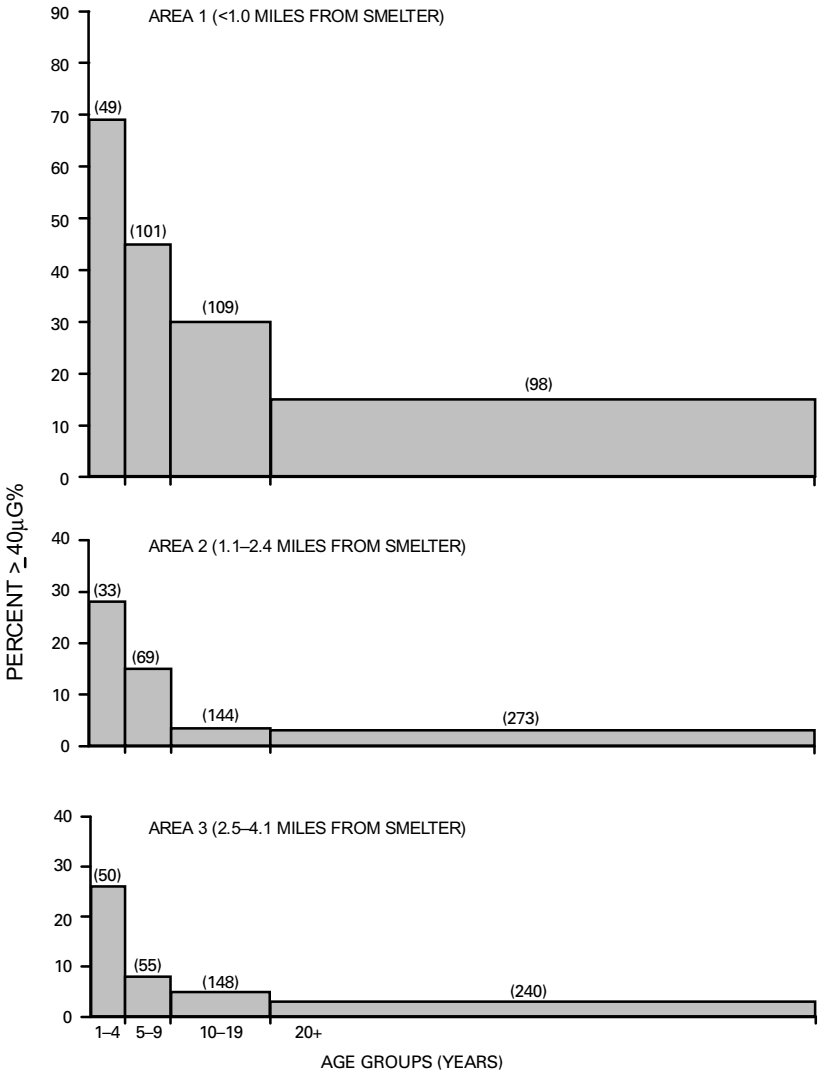


about the smelter and each with a radius of 1.0-1.5 miles. In the small, innermost stratum, all households were visited; in the 2 outer strata, approximately 2% of households were selected. Of 833 occupied households included in the survey, 672 (80.6%) were reached for the interview. A venous blood sample for lead analysis by atomic absorption spectrophotometry (AAS) was obtained from all persons up to age 20 years and from every other person above that age; samples of paint, soil, household dust, and pottery were also collected in each home for lead analysis by AAS. In all age groups, the percentage of blood levels ≥40 μG% was found to be highest in those persons living nearest the smelter (Figure 2), and the prevalence was highest in the youngest individuals; migration rates among these persons were low. In area I, 5 (8.5%) of 59 persons 1-19 years of age with blood lead levels ≥40 μG% had moved into the area in the 2 years preceding the survey. In areas II and III, the migration rate for persons 1-19 years of age with blood levels ≥40 μG% was 8.2% (4 of 49); 1 person in this group had moved from area I.

A total of 1,971 paint samples were collected for lead analysis. In area I, 9 (39.1%) of 23 children 1-4 years had exposure to at least 1 paint sample with a lead content of 1.0% or more; the comparable figures for areas II and III were 11 (33.3%) of 33 and 17 (34.0%) of 50 children, respectively. These three rates were virtually identical ($p>0.9$ by Chi-square).

Analysis of over 4,000 soil and household dust samples indicated that the mean content of lead in these specimens was significantly higher in area I than in areas II

Figure 2
PERCENT OF HUMAN BLOOD SAMPLES* WITH LEAD LEVELS ≥40 μG%, EL PASO, TEXAS — 1972



( ) NUMBER OF PEOPLE TESTED
*RANDOM SAMPLE SURVEY

and III. Furthermore, persons 1-19 years with blood lead levels ≥40 μG% were found to have been exposed to soil and dust samples with significantly higher ($p<0.001$) mean lead contents (3,264 ppm for soil, 3,522 ppm for dust) than persons with blood lead levels below 40 μG% (means: 1,032 ppm and 1,279 ppm).

Pottery vessels were used for food storage or preparation in 37 homes visited. After 1% hydrochloric acid incubation for 6 hours, 2 of 6 vessels from sector I, 6 of 19 from sector II, and 4 of 12 from sector III had a lead content ≥100 G per ml in the eluate.

(Reported by Bernard F. Rosenblum, M.D., M.P.H., Director, El Paso City-County Health Department; James M. Shoults, Acting Environmental Engineer, El Paso City-County Health Department; J. Julian Chisolm, Jr,. M.D., Chief of Pediatrics, Baltimore City Hospitals; Commu-

nity and Environmental Management Activities, Bureau of State Services, CDC; the Field Services Branch, Bureau of Epidemiology, the Toxicology Section, Clinical Chemistry, Hematology, and Pathology Branch, Bureau of Laboratories, CDC; and a team of EIS Officers.)

Editorial Note: It may be estimated from this prevalence survey, using 1970 U.S. Census data, that at least 2,700 persons 1-19 years of age in El Paso had blood lead levels ≥40 μG% at the time of the survey (Table 2). These results indicate that the problem of undue lead absorption affects persons across all of south and west El Paso to a distance of at least 4 miles from the smelter. Lead emitted by the smelter and deposited in soil and dust would appear to be the major source of the lead absorbed by humans; the accumulation in the soil and dust of emitted lead is facilitated by several features of the local environment, particularly the aridity, the sheltering effect of the high mountains, and the frequent thermal inversions. Ingestion of lead-based paint may account for a small fraction of cases of undue absorption (at most 1/3) in the youngest children. Careful neurologic and psychologic studies of persons in El Paso with blood lead levels ≥40 μG% have been conducted and are being compared with results of similar studies in a matched group with lower lead levels. This story will make it possible to ascertain objectively whether any persons are suffering subtle but possibly permanent neurologic or psychologic sequelae from prolonged lead absorption.

Control measures undertaken to date include partial reduction of smelter emission and relocation to more distant public housing of approximately 500 persons who had lived closely adjacent to the smelter property.

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Table 2
Estimated Numbers of Persons 1–19 Years With Blood Lead Levels ≥40 μG%, by Distance from Shelter
El Paso, Texas — August 1972

	Sample Group		Population 1–19 Years*	
Distance from Smelter (Miles)	No. Tested	% With Blood Lead ≥40 μG%	No. of Children	Projected No. with Blood Lead ≥40 μG%
0–1.0	259	43.2	723	312
1.1–2.4	246	11.0	12,316	1,355
2.5–4.1	253	9.5	11,486	1,091
Total	758	19.9	24,525	2,758

*1970 Census

Editorial Note—1997

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When a team of Epidemic Intelligence Service officers from CDC, led by Dr. Philip Landrigan, joined the local health department in El Paso, Texas, in March 1971 to investigate lead exposure associated with an ore smelter, the scientific understanding of pediatric lead toxicity was about to enter a period of rapid progress. Many studies

have since documented the public health threat posed by poorly controlled lead emissions from lead smelters around the world (*1*). The range of lead exposure produced in populations living near lead smelters has, in turn, facilitated studies of the mechanisms and health consequences of pediatric lead exposure.

A major objective of the El Paso investigation was to determine whether high blood lead levels (BLLs) in children were associated with smelter emissions or were explained by other lead sources also found in the community. A high level of lead emissions in a residential area was not then assumed to be a public health threat, as it is today. A 1972 National Academy of Sciences report on lead, while motivated by growing concern about widespread dispersal of lead in the environment, stated in its preface: "lead attributable to emission and dispersion into the general ambient environment has no known harmful effects" (*2*). In El Paso, the inverse gradient in air (*3*), dust, and soil contamination as one moved away from the smelter, and the parallel blood lead gradient (also found in a complementary investigation of lead exposure in Juarez, Mexico [*4*]) supported the argument that soil and dust are important vehicles of exposure. This finding foreshadowed subsequent research demonstrating the pathway from lead in soil and dust to lead contamination of hands to lead in blood, presumably from normal hand-to-mouth behavior and ingestion of contaminated soil and dust (*5–7*).

In 1975 and 1976, CDC investigators, led by Dr. Edward Baker, documented the potential for exposure to leaded dust among children of workers at a secondary lead smelter in Tennessee (*8*). Their findings and those of other investigations of "take-home" lead exposure that followed brought about provisions in the 1978 Occupational Safety and Health Administration (OSHA) standard for occupational lead exposure requiring hygienic measures in general industry to prevent lead workers from carrying lead dust home on their skin, shoes, and clothing (*9*).

In the 1960s and 1970s, children living near smelters or in the households of smelter workers were only a small part of a widespread national problem of "undue lead absorption" (*10*). In urban areas, deteriorated lead paint in older housing made the problem especially acute. In the same year as the El Paso survey, a door-to-door survey of inner-city children in Rochester, New York, found a mean BLL of 44 μg/dL (*5*), which was close to that measured near the El Paso smelter.

Since the early 1970s, it also has become more clear that lead is a multimedia contaminant and that demonstrating the importance of a given source does not rule out the contribution of other sources. For example, data from the Second National Health and Nutrition Examination Survey (NHANES II) conducted from 1976 through 1980 indicated that the mean BLL among children aged <6 years residing in rural areas was 14 μg/dL (average levels were 3–6 μg/dL higher among children living in more urbanized areas) (*11*). During the same period, widespread population exposure to lead emissions was reflected in average BLLs that declined in close parallel to the decreasing consumption of leaded gasoline (*12*). Thus, children living near the El Paso smelter, children in the homes of lead workers, and children in downtown Rochester probably shared with children across the country a contribution to their BLLs from lead in gasoline. Local sources, added to the higher background exposure prevalent at the time, resulted in BLL distributions that are extremely high by today's standards.

Perhaps the most telling indication of how the scientific view of lead exposure has changed since 1971 is that, in 1971 "undue lead absorption" referred only to BLLs

≥40 μg/dL. Numerous subsequent studies documented that BLLs much lower than 40 μg/dL, then considered acceptable, adversely impact the health of children without causing overt symptoms. For example, investigators from CDC's Bureau of Epidemiology, again led by Dr. Landrigan, found an inverse relation between BLLs and nerve conduction velocities among children exposed to emissions from a smelter near Kellogg, Idaho (*13*). As the decade closed, Dr. Herbert Needleman's landmark study was published, demonstrating lower cognitive test scores and higher teachers' ratings of behavioral problems among children with higher tooth lead levels but no history of clinically overt lead poisoning (*14*).

Epidemiologic studies identified subclinical effects of lead by comparing the health of children with different levels of lead exposure. For most U.S. populations studied in the 1970s, the least exposed children had BLLs well above the average in the U.S. population today. Thus, health effects at lower levels could not be detected. As population BLLs decreased through the 1980s, careful prospective studies found subtle effects of lead on learning and behavior at BLLs well below those of the least exposed children in El Paso (*15*).

In addition to contributing to scientific knowledge about lead exposure and its effects on health, findings from the El Paso survey and others precipitated measures to reduce emissions at lead smelters. In 1977, a follow-up investigation by CDC and the El Paso Health Department found that BLLs among children living nearest the smelter had decreased by approximately 50% (*16*). More importantly, the El Paso survey was a prelude to a large body of continuously refined epidemiologic investigations that provided the impetus for actions to dramatically reduce population lead exposure from lead in gasoline, soldered food cans, drinking water conduits, and other sources in the United States. As a result, mean BLLs among children have declined nationally by >80% overall and by similar amounts in population subgroups defined by age, race, ethnicity, income levels, and urbanization (*17,18*). More recently, international agreements to reduce the use of leaded gasoline may bring about significant reductions in worldwide lead exposure. Ironically, the unfortunate epidemics of lead toxicity near smelters in El Paso and elsewhere ultimately enabled more rapid progress in understanding and controlling lead exposure than might otherwise have been possible.

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Angiosarcoma of the Liver Among Polyvinyl Chloride Workers — Kentucky

MMWR 1974;23:49–50 (February 9, 1974)

Between September 1967 and December 1973, 4 cases of angiosarcoma of the liver were diagnosed among men employed in the polyvinyl chloride polymerization section of a B.F. Goodrich plant near Louisville, Kentucky. This section of the plant began operations in 1938. It employs about 270 persons and produces polyvinyl chloride as well as a variety of copolymers by polymerization of vinyl chloride monomer. All 4 men had worked continuously in the section for at least 14 years prior to onset of illness (Table 1); all 4 had worked directly in various phases of the polymerization process.

Case 1 presented in August 1967 with an epigastric mass and thrombocytopenia. An exploratory laparotomy was performed in September 1967; liver biopsy revealed angiosarcoma. Case 2 presented in January 1970 with gastrointestinal (GI) bleeding. Recurrent bleeding in May 1970 led to an exploratory laparotomy at which time a diagnosis of angiosarcoma was made on liver biopsy. Case 3 presented in January 1964 with GI bleeding which recurred in May 1965 with signs of portal hypertension. A portacaval shunt was performed, and liver biopsy yielded a diagnosis of cirrhosis. Repeat biopsies in October 1970 and September 1972 confirmed this diagnosis. Autopsy in March 1973 revealed angiosarcoma. Case 4 presented in July 1973 with hepatosplenomegaly, weight loss, and jaundice. Two liver biopsies were interpreted as showing severe cirrhosis. Autopsy in December 1973 revealed angiosarcoma.

In each case, pathologic material revealed the presence of extensive cirrhosis of a non-alcoholic type in addition to angiosarcoma. In 2 cases, the diagnosis of angiosarcoma was made only at autopsy, cirrhosis having been diagnosed 7 years before in Case 3 and 5 months before in Case 4. None of the patients gave histories of prolonged alcohol use or exposure to hepatotoxin outside their work place. In particular, none had ever had exposure to thorium dioxide or to arsenic, two materials known specifically to induce hepatic angiosarcoma in man (*1,2*).

Table 1
Cases of Angiosarcoma of the Liver among Polyvinyl Chloride Workers
B.F. Goodrich Plant
Louisville, Kentucky

Case	Age at illness onset	Date of			Years worked with PVC before illness
		Illness onset	Diagnosis	Death	
1	43	Aug. 1967	Sept. 1967	Jan. 7, 1968	17
2	36	Jan. 1970	May 1970	Sept. 27, 1971	14
3	41	Jan. 1964	Mar. 1973	Mar. 3, 1973	14
4	58	July 1973	Dec. 1973	Dec. 19, 1973	27

(Reported by John Creech, M.D., Plant Physician, B.F. Goodrich Chemical Company, Louisville, Kentucky; Maurice N. Johnson, M.D., Director of Environmental Health, B.F. Goodrich Chemical Company, Akron, Ohio; Bradford Block, M.D., Medical Consultant, Kentucky Occupational Safety and Health Administration, Kentucky State Department of Labor; National Institute for Occupational Safety and Health, and the Cancer and Birth Defects Division, Bureau of Epidemiology, CDC.)

Editorial Note: Angiosarcoma of the liver is an exceedingly rare tumor. It is estimated that only about 25 such cases occur each year in the United States. Four cases, therefore, among a small number of workers at a single plant is a most unusual event, and one which raises the possibility of some work-related carcinogen, conceivably vinyl chloride itself. Although no data are yet available concerning the occurrence of angiosarcoma among workers at other vinyl chloride plants in the United States, it seems distinctly possible that the problem may be industry-wide. Epidemiologic studies have started to determine the extent of the problem in the United States, with respect both to angiosarcoma of the liver and to its possible relationship to post-toxic cirrhosis.

Published data concerning the potential hepato-toxicity and oncogenicity of vinyl chloride are limited. Studies in Germany have suggested a link between hepatic damage and occupational exposure to vinyl chloride (*3*), while Italian workers have suggested that vinyl chloride may cause a wide variety of tumors in animals (*4*). The chemical concentrations used in these latter experiments, however, far exceed levels likely to be encountered in industrial environments. Efforts to confirm such observations and to measure effects at lower dose levels are now in progress.

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Editorial Note—1997

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Workers constitute the segment of the U.S. population most heavily exposed to chemical toxins and physical agents. Because of their intense and prolonged exposures compared with the general public's, workers generally develop illnesses of toxic etiology more frequently, more quickly after the introduction of new chemical compounds, and in more severe forms.

Work-related diseases encompass a broad range of human illness (*1*). For example, chronic bronchitis frequently occurs in coal miners; skin cancer in farmers; bladder cancer in dye workers exposed to aniline compounds; leukemia and lymphoma in chemical workers exposed to benzene; kidney failure in lead workers; impaired reproductive function in workers exposed to lead and certain pesticides; and chronic disorders of the musculoskeletal system in workers who sustain repetitive trauma.

The diagnosis of occupationally associated disease often is difficult (*2*). For most diseases, a case of occupational origin is not clinically distinguishable from illness resulting from other etiologies. Informed suspicion is therefore essential to recognize occupational disease, and a careful history of occupational exposure is the critical diagnostic instrument. In the initial diagnostic interview of each new patient, the physician must obtain at least a brief history of occupational exposures. Modification of the concept of the sentinel health event (SHE) (*3*) has further assisted physicians in establishing linkages between occupational exposures and disease (*4*).

A SHE has been defined as "an unnecessary disease, disability, or untimely death whose occurrence signals a failure of prevention" (*3*). Examples in general medicine include maternal deaths during childbirth, outbreaks of cholera, or a single case of poliomyelitis. To extend the concept of the SHE to the workplace, a "sentinel health event (occupational)" (SHE[O]) is analogously defined (*4*) as "an unnecessary disease, disability or untimely death which is occupationally related." Recognition of a SHE(O) requires clinical astuteness and attention to the exposure history. Typically, the occurrence of a SHE(O) stimulates further investigation or research and may trigger regulatory or other targeted preventive action.

This *MMWR* report on angiosarcoma of the liver in vinyl chloride polymerization workers represents a splendid description of a SHE(O). This report marked the first recognition of the carcinogenicity to humans of vinyl chloride monomer (VCM), the highly reactive gas to which workers were exposed in the B.F. Goodrich plant near Louisville, Kentucky. The initial observation was made by John Creech, M.D., the plant physician, and Maurice Johnson, M.D., the corporate medical director. These physicians had evaluated three men with angiosarcoma of the liver during a 2-year period (*5*). They realized, through careful history-taking, that all of the men with this rare malignancy were employed in the same department of the plant.

Publication of this report and a related journal article (*5*) stimulated a series of clinical investigations, epidemiologic studies, and toxicologic analyses. Henry Falk, M.D., an Epidemic Intelligence Service (EIS) officer in the Cancer and Birth Defects Division in CDC's Bureau of Epidemiology, was assigned by his Division Director, Clark W. Heath, Jr., M.D., to investigate this outbreak. Working with Richard Waxweiler, Ph.D., of the National Institute for Occupational Safety and Health, Hans Popper, M.D., of the Mount Sinai School of Medicine, and Louis Thomas, M.D., of the National Cancer Institute, Dr. Falk confirmed the existence of the outbreak and also discovered a premalignant lesion—idiopathic hepatic fibrosis—in additional members of the population heavily exposed to vinyl chloride monomer (VCM) (*6*). This work stimulated a major international conference that was convened at the New York Academy of Sciences by Irving Selikoff, M.D. (*7*), at which the carcinogenicity of VCM was confirmed. VCM is now universally considered to be a highly potent chemical carcinogen (*7*).

This recognition of the carcinogenicity of VCM also stimulated intense regulatory activity (*8*). To prevent future cases of VCM-associated angiosarcoma, the Occupational Safety and Health Administration in 1974 proposed a 500-fold reduction in the occupational exposure standard for VCM gas—from 500 parts per million (ppm) in air to 1 ppm. The plastics-manufacturing industry immediately objected that such reduction was not possible and would drive the vinyl chloride polymerization industry overseas. An industry-sponsored study estimated that the costs to comply with the proposed new standard would exceed $25 billion (*8*). Within the year, however, a ma-

jor plastics manufacturer announced development of a novel closed-loop polymerization process that greatly reduced atmospheric releases of VCM and almost completely eliminated worker exposures. The manufacturer patented this system and subsequently licensed it to other manufacturers at substantial profit. The VCM standard of 1 ppm remains in force today (*9*) and is readily achieved in the workplace. New cases of hepatic angiosarcoma in vinyl chloride polymerization workers have been virtually eliminated (*10*).

This episode, one of the earliest reports of an occupational disease outbreak published in the *MMWR*, underscores the importance of informed clinical observation in the recognition of work-related illness. Furthermore, the regulatory actions precipitated by this report and the ensuing investigation of this episode illustrate that a safe working environment and economic progress are not mutually exclusive. When well-conceived protective standards are accepted with good will and ingenuity is used to encourage compliance with those standards, then job safety, economic advances, and a healthy environment can comfortably co-exist.

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IUD Safety: Report of a Nationwide Physician Survey

MMWR 1974;23:226,231 (June 29, 1974)

In an attempt to determine the morbidity and mortality associated with IUD use nationwide, the Family Planning Evaluation Division, CDC, in conjunction with the Committee on Maternal and Child Care of the American Medical Association (AMA) and the American Osteopathic Association (AOA), began a physician survey in June 1973.

From their master files, AMA and AOA provided the names of 34,544 physicians in the United States and Puerto Rico – virtually all physicians who had a primary, secondary, or tertiary interest in obstetrics or gynecology, or a primary interest in family practice, public health, or general preventive medicine. In the last week of June 1973, CDC sent a questionnaire to all physicians on the list inquiring about women who had been hospitalized or had died with possible complications related to the use of an IUD in the preceding 6 months. Physicians were asked to check 1 or more of 8 diagnostic categories for their patients such as complicated pregnancy, uterine perforation, and hemorrhage. After a second mailing of the same questionnaire to physicians who had not responded by August 1, a total of 16,994 responses (49.2%) were received by January 2, 1974. Subsequently, a 1% probability sample was drawn from the 17,550 non-respondents; field officers were successful in obtaining information about IUD complications from 173 of 176 practices by telephone and personal interviews.

Physicians responding by mail provided 3,502 net, unduplicated case reports of women hospitalized in the first 6 months of 1973. After correction for the non-respondent physicians, approximately 7,900 IUD-associated hospitalizations were estimated to have occurred in this period. Using an estimate by the Family Planning Evaluation Division of approximately 3.2 million IUD wearers in early 1973, the calculated rate of IUD-related hospitalizations was 5 per 1,000 woman-years of IUD use.

While the small number of IUD-related deaths is insufficient to demonstrate an increased mortality rate associated with any specific type of device, the overall rate of IUD-related mortality appears to be low compared with the mortality rates associated with pregnancy and other forms of contraception *(1)*. Five fatalities were reported in the 6-month study period by the 16,994 physicians who responded by mail and the documenting details of each of these cases supported the suggestion that an IUD had contributed to the death. Four of the 5 terminal illnesses involved severe infection; 2 of these 4 infections involved a pregnancy. The devices used by these women were 2 Lippes Loops*, 2 Saf-T-Coils*, and 1 Dalkon Shield*. These 5 reports imply a minimum IUD-related mortality rate of approximately 3 per million woman-years of use.

*Inclusion of trade names does not imply endorsement by the Public Health Service or the U.S. Department of Health, Education, and Welfare.

** $$\text{Odds Ratio} = \frac{\left(\frac{\text{Dalkon Shield}}{\text{All Other IUDs}}\right)\ \text{pregnancy related}}{\left(\frac{\text{Dalkon Shield}}{\text{All Other IUDs}}\right)\ \text{not pregnancy related}}$$

Of the 3,473 reports which included diagnoses, 2,932 also specified the type of IUD involved. A relative excess of Dalkon Shield IUDs was observed among case reports carrying the diagnosis of "complicated pregnancy" (Table 1). The crude odds ratio** for all the cases in Table 1 is 2.1 ($p<.001$). Separate stratifications by the patient's age, race, and geographic region show a comparable elevation of the same odds ratio for each group. When the case reports were stratified by the size of IUD, the odds ratio for the 180 women with nulliparous-sized IUDs was not significantly different from 1.0, but was 2.0 and 2.2 for the parous (standard) and unknown sizes, respectively, both statistically significant.

Table 1
Association Between the Dalkon Shield and Complicated Pregnancies Among Women Hospitalized for IUD-Related Complications*

	Type of IUD					
Diagnosis of Complication	**Dalkon Shield**		**All Other IUDs (incl. Unknown)**		**Total**	
Pregnancy Related	538	(53.9%)	461	(46.1%)	**999**	**(100.0%)**
Not Pregnancy Related	887	(35.9%)	1,587	(64.1%)	**2,474**	**(100.0%)**
Total	**1,425**	**(41.0%)**	**2,048**	**(59.0%)**	**3,473**	**(100.0%)**

*Table excludes 29 case reports with unknown diagnosis.

The 1% sample of non-respondent physicians who were interviewed in person or by phone furnished 60 unduplicated case reports. The crude odds ratio for these reports was 8.3 ($p=.0049$), establishing that a statistical association between the Dalkon Shield and complicated pregnancies also existed in the experience of these physicians.

Since the use prevalence of the various IUD types in early 1973 is unknown, it is impossible to draw any firm conclusion about the morbidity rates associated with each device. The magnitude of the odds ratio is influenced not only by the relatively large number of Dalkon Shields involved in complicated pregnancies (numerator of the odds ratio) but also by the relatively small number of Dalkon Shields involved in complications in non-pregnant women (denominator of the odds ratio). If the Dalkon Shield accounted for more than 41% (Table 1) of the IUDs in use early in 1973, then the observed elevation in the odds ratio might be better explained by a relatively low rate of hospitalizations for non-pregnant complications associated with this type of IUD. Such a high use prevalence of the Dalkon Shield is very unlikely based on CDC's review of sales data furnished by the major IUD manufacturers. The relative excess of women hospitalized with complicated pregnancies associated with the standard-sized Dalkon Shield could possibly be explained by an elevated rate of pregnancy with this device, by an increased rate of complications once a pregnancy is established, or by a combination of these postulated factors.

(Reported by the Committee on Maternal and Child Care of the American Medical Association; the American Osteopathic Association; and the Family Planning Evaluation Division, Bureau of Epidemiology, CDC.)

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Editorial Note—1997

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Since the mid-19th century when Ignaz Semmelweiss, Oliver Wendell Holmes, and others showed that puerperal fever was both contagious and preventable, epidemiology has been useful as an effective tool to assist in improving reproductive health. CDC first applied epidemiology to family-planning evaluation and reproductive health in the early 1960s when new female fertility-control measures had become available. Oral contraceptives and plastic intrauterine contraceptive devices (IUDs) provided promising new opportunities for family planning. CDC leaders, especially Alexander D. Langmuir, M.D., Chief Epidemiologist, had both enthusiasm and concern about these opportunities. Evidence for the effectiveness of the new methods of contraception was emerging, but potential adverse effects remained largely unevaluated. Of specific concern to Langmuir was the possible relation between IUD use and pelvic infection. Therefore, in 1964, CDC assigned Nicholas Wright, M.D., an officer in CDC's Epidemic Intelligence Service (EIS) program, to Grady Memorial Hospital, a public institution in Atlanta, Georgia, with a large ambulatory-care clinic and approximately 1000 beds, to investigate the safety of the IUD. Work by Wright and others determined that women with IUDs had pelvic infections at a higher rate than expected but that most of these women could be treated effectively and without serious complications.

A decade later, the *MMWR* of June 29, 1974, raised questions about the safety of the Dalkon Shield, an IUD marketed during 1970–1974. Both the AMA and the AOA collaborated with CDC to conduct this survey of physicians in June 1973. Analysis of the case reports supplied by the survey respondents showed an excess risk for complicated pregnancies among Dalkon Shield users, compared with users of other IUDs (*1*). In 1974, the manufacturer withdrew the device from the marketplace.

In 1975, CDC reported that Dalkon Shield users were more likely than users of other IUDs to die from spontaneous abortions (*2*). Reports of mid-trimester septic abortions associated with the Dalkon Shield hastened the passage of the Medical Device Amendments of 1976, which gave the Food and Drug Administration (FDA) greater control over medical devices. In 1983, CDC reported that Dalkon Shield users had a greater risk for pelvic inflammatory disease than users of other types of IUDs and non-IUD users (*3*). In that same year, CDC and FDA recommended that women still using Dalkon Shield IUDs have them removed. The experience with the Dalkon Shield has had a dramatic negative impact on the further use of IUDs in the United States and has affected the pharmaceutical industry, physicians, and women who otherwise might find the IUD an acceptable method of contraception (*4,5*).

IUDs, first used in Germany and Japan in the early 1900s, showed great promise after their reintroduction in 1960 as biologically inert plastic devices (*6*). Thereafter, a

large variety of devices were produced as manufacturers attempted to identify the ideal device. The most important recent advance was the development of the medicated devices, particularly the copper-bearing IUDs (*7*). The most commonly used IUD in the United States today—the Copper T380A—has a low rate of side effects and is perhaps the most effective IUD in use internationally, with a pregnancy rate of ≤1% per year (*8*). In Europe, the levonorgestrel-releasing device also is associated with few side effects, very low failure rates, and reduced menstrual blood flow because of intrauterine progestin effect (*9*). This device has not been introduced into the United States. As a result, the only progesterone-releasing device available in the United States requires change of the device annually and is rarely used in this country.

During the 1980s, the noncopper-bearing devices popular in the 1960s and 1970s were withdrawn from the market for economic reasons (*4*). In 1986, manufacturers also removed copper-bearing devices from the market—not because of new information about risks, but because of the heavy financial burdens imposed on the manufacturers by issues related to liability (*4*).

The major safety concern associated with the use of IUDs has been the risk for developing pelvic inflammatory disease (*10*). Recent studies have suggested, however, that most cases of pelvic infection that occur with an IUD in place are attributable to sexually transmitted diseases (STDs) (*11,12*) and that women at low risk for STDs also are at low risk for pelvic infection while they are using an IUD. Further evidence that the IUD is associated with low risk for pelvic infection is documented by a study of infertility in which IUD users with one sexual partner were at no greater risk for infertility than nonusers of the IUD (*13*). Most IUD-attributable infections appear to be related to insertion of the device (*12*); some of these infections probably are preventable with proper infection-control measures, and trials of the effectiveness of administering prophylactic antibiotics at the time of insertion are in progress.

The 1974 *MMWR* and subsequent reports by CDC identified an increased risk for infectious morbidity related to use of an IUD that is no longer marketed. Subsequent epidemiologic studies of the safety of currently available devices indicate that women at low risk for STDs are at low risk for pelvic infection with IUD use.

In the United States, nearly 60% of pregnancies are unintended (*14*), and many women wanting to prevent unintended pregnancy are appropriate candidates for IUD use. Despite evidence that the long-term effectiveness of the Copper T380A device is similar to that of tubal sterilization (*15,16*), <1% of women using contraceptives in 1995 were using this device (*17*). Among the small number of women using IUDs, however, acceptance of this method is high: in 1992, for example, 96% of IUD users viewed their method favorably, compared with 94% of oral contraceptive users, 93% of those who chose male or female sterilization, 76% of diaphragm users, and 74% of rhythm methods users (*18*). Women desiring long-term effective contraception and their clinicians should be aware that currently marketed IUDs are highly effective and acceptable and are associated with a low risk for complications in women at low risk for STDs.

In addition to highlighting the commemoration of CDC's 50th anniversary, reprinting this 1974 *MMWR* coincides with and highlights the 30th anniversary of CDC's Division of Reproductive Health. In 1967, the Family Planning Evaluation Activity (FPEA)—which authored the 1974 report—was established in CDC's Bureau of Epidemiology, becoming one of CDC's earliest noninfectious disease program

areas. The FPEA began with only four staff members; today, the staff consists of 160 members in what is now the Division of Reproductive Health, part of CDC's National Center for Chronic Disease Prevention and Health Promotion. In 1970, the FPEA became the Family Planning Evaluation Division, and the division quickly became a focus of excellence within CDC, helping to introduce and disseminate further the concepts of analytic epidemiology eventually adapted by acute/infectious disease programs. From 1967 (when the division first assigned EIS officers to evaluate family-planning programs in state health departments) to the present, the links between the division and the EIS have been crucial at CDC in helping to introduce CDC's methods of applied/field epidemiology to the challenges of reproductive health, both nationally and internationally. The three decades of history of the division reflect the creative and effective use of epidemiology for the promotion of reproductive health.

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Original report published with new editorial note in *MMWR* 1997;46:969–74 (October 17, 1997).

Acute Childhood Leukemia — Columbus, Ohio

MMWR 1976;25:77–8 (March 19, 1976)

From August–October 1975, 8 cases of acute leukemia were diagnosed at Columbus Children's Hospital in Columbus, Ohio, in children living in that city. During any consecutive 3-month period in 1972–1974, the greatest number of cases of acute leukemia diagnosed at this hospital in Columbus children was 4 (Figure 1).

To evaluate this cluster of illness, all cases of acute leukemia diagnosed at Columbus Children's Hospital in 1972–1975 were reviewed with respect to age, race, sex, type of leukemia, date of diagnosis, and residence in and outside of Columbus (Table 1). The hospital provides care for most children with leukemia in Columbus and for many such patients from surrounding areas. In the 3-year period 1972–1974, an average of 5.3 cases of acute childhood leukemia were seen each year among Columbus residents (the expected number is 6.1, based on age-specific rates from the Third National Cancer Survey [*1*]). Over the 4-year period 1972–1975, 107 cases were seen, 28 among Columbus residents. Both Columbus and non-Columbus patients in 1975 were somewhat older and included relatively more females than in earlier years. Case distributions by race and leukemia cell type were not unusual.

FIGURE 1. Acute Leukemia, Columbus Children's Hospital, 1972–1975 — by Place of Residence and Date of Diagnosis

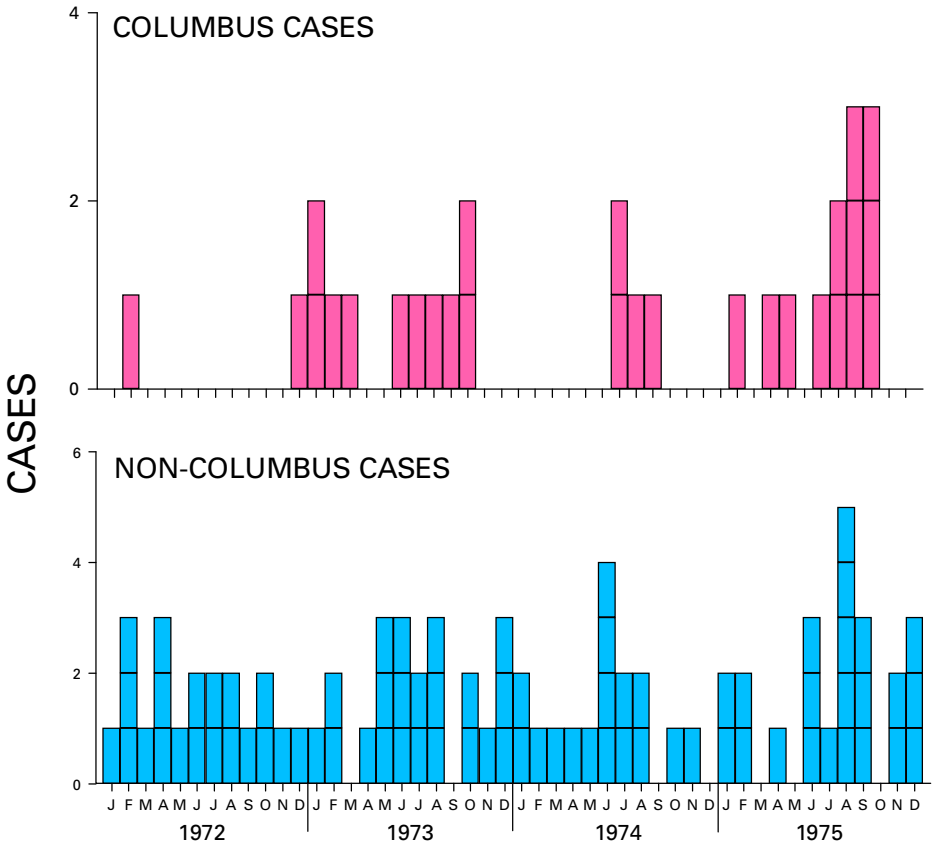

TABLE 1. Acute Leukemia, Columbus Children's Hospital, 1972–1975 — By Age, Sex, Race, Place of Residence, and Year of Diagnosis

	Year of Diagnosis			
	1972–1974		1975	
	Columbus Residents	Other	Columbus Residents	Other
Total number of cases	16	57	12	22
Mean age at diagnosis	4.5	5.4	7.0	6.5
Sex: Male	10	33	5	11
Female	6	19	7	11
Race: White	13	55	9	21
Black	3	2	0	1
Other	0	0	1	0
Unknown	0	0	2	0
Leukemic Cell Type:				
Myelocytic	3	11	3	4
Monocytic	2	2	0	0
Lymphocytic or Stem Cell	11	44	9	18

Twelve cases were diagnosed in Columbus residents in 1975, compared with a total of 16 for all 3 preceding years. To assess the possibility of time-space clustering among Columbus cases over the entire 4-year period a statistical analysis was performed using the procedure devised by Knox (*2*). No statistically significant clustering was found; 13 case-pairs were observed in which dates of diagnosis were less than 1 year apart and places of residence 1 mile or less apart, whereas 14.4 pairs were to be expected on a random basis. Inspection of the 1975 case data showed no geographic clustering and no obvious community or family interrelationships among cases. No evidence of seasonal periodicity was found on statistical testing by month of diagnosis for pooled data from all 4 years.

Reported by I Ertel, MD, W Newton, MD, Children's Hospital, Columbus, Ohio; TJ Halpin, MD, MPH, State Epidemiologist, Ohio Department of Health; Field Services Div and Cancer and Birth Defects Div, Bur of Epidemiology, CDC.

Editorial Note: The question of time-space clustering among cases of leukemia and lymphoma has received considerable epidemiologic attention, particularly in connection with hypotheses regarding the possible viral etiology of cancer. While no evidence has been found of statistically significant time-space clustering among adult cases, several studies have suggested such a tendency among cases of childhood acute leukemia (*2–5*). The significance of such observations remains unclear. In the present investigation no evidence, statistical or otherwise, was found to suggest that the recent case cluster in Columbus might be due to factors other than chance. Further investigations of such clusters may be desirable, however, as a potential source of clues regarding the etiology of childhood tumors.

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Burkitt's Lymphoma — Winchester, Virginia

MMWR 1976;25:173 (June 11, 1976)

Three cases of Burkitt's lymphoma (BL) have occurred since 1971 in young boys living in one residential section of Winchester, Virginia. Onset of illness in the first 2 cases (ages 9 and 15) occurred simultaneously in August 1971 (*1*); the third patient (age 8) first became ill in July 1975.

The first 2 patients lived 2 houses apart and the third one-half mile away. None of the 3 patients or their families was acquainted or shared common community activities, although all 3 boys had attended the same grade school at different times. All 3 patients were Caucasian.

Manifestations of disease were similar in all 3 cases. Initial symptoms in each case involved persistent sore throat progressing to peritonsillar masses in the first 2 cases and to cervical adenopathy in the third. Histologic diagnosis of BL was made on biopsy of these masses and was confirmed on pathologic review at the National Cancer Institute. Marrow aspiration was suggestive of leukemic transformation in the third case, but not in the first 2. In each case there was clinical evidence of central nervous system (CNS) tumor involvement. Despite intensive chemotherapy in all 3 cases, and radiation therapy in 2, disease was unremitting and led to death 1, 4, and 7 months after initial diagnosis. Autopsy findings in the first 2 cases showed widespread tumor involving the CNS, as well as cervical and abdominal lymph nodes. In the third case, autopsy showed residual tumor only at the original site of occurrence (the neck). Serum antibody against Epstein Barr virus (EBV) was present at low titers in 2 cases.

Epidemiologic investigation revealed no clues to suggest a possible common etiology for these cases beyond their closeness in time and place of occurrence. Although the summers of 1971 and 1975 had somewhat greater rainfall than other years, no evidence was found to link the cases to increased mosquito or other insect exposures. No unusual local patterns of leukemia, lymphoma, or infectious mononucleosis incidence were found, and no other persons with childhood cancer were identified as having been in contact with the patients or being in their particular neighborhood.

Reported by N McWilliams, MD, Medical College of Virginia; W Hatfield, MD, Lord Fairfax Health District; R Jackson, MD, State Epidemiologist, Virginia State Dept of Health; and Cancer and Birth Defects Div and Field Services Div, Bur of Epidemiology, CDC.

Editorial Note: Burkitt's lymphoma is extraordinarily rare outside certain parts of central Africa and New Guinea where it constitutes the most common tumor of childhood (*2*). Epidemiologic surveys of childhood cancer in the metropolitan areas of Atlanta, Georgia, and Houston, Texas, suggest that the annual incidence of BL in the United States is in the range of about 1 case per million children, or an expected incidence of about 1 case every 200 years for a town the size of Winchester. In this context, the occurrence of 3 cases over 5 years in one neighborhood is distinctly unusual.

The etiologic significance of such case clustering is not clear. While early studies of African BL suggested that time-space case clustering was a common feature of the disease (*3*), more recent epidemiologic work has cast doubt on the idea (*4*). Current evidence suggests that the etiology of African BL may be related to EBV infection in a host whose immunologic state has been severely affected by constant and severe malarial infections (*5*). The present cases, however, provide no obvious clinical or epidemiologic clues regarding their particular etiology.

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Editorial Note—1997

Clark W Heath, Jr, MD, Vice President for Epidemiology and Surveillance Research, American Cancer Society, Atlanta, and former Director, Division of Chronic Diseases, Center for Disease Control. Glyn G Caldwell, MD, Clinical Coordinator, Indiana Medical Review Organization, Indianapolis, and former Chief, Cancer Branch, Bureau of Epidemiology, Center for Disease Control.

Public concern can quickly rise when persons perceive an excess of cancer in their local community. Such situations are not infrequent. Each deserves prompt public health attention to address community concerns and to explore possible etiologic clues. However, it is difficult to know when field investigations are needed and how far they should proceed. The problem is neither new nor unique to cancer because similar concerns arise about other chronic or noninfectious diseases. Cases can cluster simply by chance, and random case distributions probably account for most community case clusters. It is possible that certain clusters may have community-based causes, possibly resulting from particular patterns of infectious disease occurrence or from environmental exposures. Although methodologic problems greatly limit the exploration of such possibilities, carefully designed field investigations in selected situations should be considered (*1,2*).

Reports of such investigations about cancer clusters have appeared in *MMWR*. The two reports reprinted in this issue illustrate the diversity of analytic approaches that have been used, as well as the uncertainty of conclusions. Both of these investigations involved collaborative efforts between CDC (the Chronic Diseases Division and the Field Services Division) and local/state medical and public health authorities. In the case of acute childhood leukemia in Columbus, Ohio (*3*), concern was for disease frequency in the city as a whole after eight cases were diagnosed during a 3-month period—twice the maximum number seen before. However, after further investigation, no features were observed that distinguished these cases from others, and a statistical analysis of time-space closeness indicated no evidence of unusual clustering.

The appearance of Burkitt's tumor in Winchester, Virginia, presented a different problem (*4*). This particular cancer is rare outside central Africa and New Guinea, and the two initial cases occurred in children whose diagnoses were simultaneous and who lived only two doors apart. The third patient, diagnosed 4 years later, lived nearby. Although no other links were found among the three cases, the rareness of the tumor, the time-space closeness of the first two cases, and the recurrent pattern suggested by the third case required consideration of alternate explanations to that of a chance event.

Interest in cancer case clusters has been evident in the medical literature since the late 19th century. Leukemia has received particular attention, perhaps because clusters suggest infectious disease outbreaks and because white cell elevations are associated with infection. The focus on leukemia intensified in the 1960s when tumor virologists, after demonstrating that leukemia viruses exist in other species, initiated an extensive search for such viruses in humans. During the 1960s and 1970s, CDC played a prominent role in that search by working closely with the National Cancer Institute in field investigations of leukemia case clusters. One of the earliest of these investigations involved eight cases of childhood leukemia in the Chicago suburb of Niles, Illinois (*5*). Seven of those cases were associated with one particular school where a parallel pattern of rheumatic-like illness had simultaneously appeared. The neighborhood was newly created, a situation later recalled when observations concerning a childhood leukemia cluster in the United Kingdom (UK) suggested that risk might be heightened in newly established communities (*6*).

Epidemiologic work continued at CDC into the 1980s, with several field investigations conducted each year in cooperation with various local and state health departments (*7*). Most studies involved time-space clusters of childhood leukemia cases in residential communities; however, some work involved adult leukemias, cancers of other types in both adults and children, multiple-case families, associations between human and animal cancers (i.e., pets and farm animals), and cancers occurring within acquaintance networks (e.g., former school mates). In addition, occasional situations were studied in which case clusters involved congenital malformations or chronic neurologic disease. Over time, emphasis gradually moved away from infectious disease hypotheses and increasingly focused on environmental exposures (e.g., hazardous waste sites, water pollution, and ionizing radiation).

In recent years, interest has been revived about clusters of childhood leukemia in residential communities. Much of the impetus has come from studies in the UK where a cluster of five cases occurred in a small town affecting children of men employed at a nearby nuclear fuel-reprocessing plant. Extensive epidemiologic studies confirmed this local increase in incidence and suggested a possible relation to increased paternal exposure to low levels of ionizing radiation in the workplace before the children were conceived (*8*).

Although studies in other human and experimental settings have not confirmed this association, nationwide studies of childhood leukemia in the UK have suggested that risk may be increased in newly settled towns, such as the one near the nuclear reprocessing plant. This observation has led to the hypothesis that infectious disease patterns among children in such new towns may be less stable than in more settled communities and may, on occasion, be reflected in unusual patterns of childhood leu-

kemia as a rare sequel to certain infections (*6*). Again, this concept recalls the earlier Niles, Illinois, experience.

Despite frequent attention over the years to individual cancer case clusters and despite the various hypotheses generated, there has been no instance yet where a biologic cause for clustering has been convincingly demonstrated. In the rare instance when causation has been proven from studies of small groups of cases (*9*), virtually all have involved rare tumors in occupational settings where exposures were high and where reasonable evidence existed to establish individual exposure levels. The most striking example involved vinyl chloride monomer exposures causing hepatic angiosarcomas in vinyl chloride polymerization workers (*10,11*). No comparable set of data can be cited for exposures hypothesized in residential settings.

There are clear reasons why community cluster studies are generally inconclusive. When known carcinogens are in question (either chemicals or ionizing radiation), exposures are usually very low. Many situations, however, focus on exposures, such as nonionizing radiation, for which firm evidence of carcinogenicity is lacking at any dose. Studies also are limited by the long and irregular latency of cancer, the clinical nonspecificity of cancer cases (e.g., our inability to assign specific causes to individual cases), and the relative rareness of disease at any one point in time, resulting in very small numbers on which to base epidemiologic analyses. Nonetheless, public health departments must respond in some manner when cancer case clusters come to their attention. The first step is to respond quickly and openly so that communication with community residents is effective and concerns are not neglected. The second step is to confirm the accuracy of reported diagnoses and to compare the number of observed cases with the number to be expected. Often investigations need go no further. If more work is needed, however, the next step is either to interview affected patients or their families in search of common life features or to design and conduct a more formal epidemiologic study, usually a case-control design. Here the work may not be worth the effort unless a reasonable etiologic hypothesis exists or community concern is exceptionally high. The methodologic difficulties become all too apparent, especially the weakness of such studies, limited as they are by very small numbers. Environmental studies also should be approached with caution because of their weakness in establishing clear case-exposure relations and because of their great expense.

Despite these analytic limitations, cancer case clustering deserves research attention. With the possibility of molecular marker techniques, which in the future may help determine the etiologies of individual cancer cases, it may be possible to conduct useful studies of selected clusters, whether the hypotheses are infectious or environmental. Still, the rarity of nonchance clusters must always be considered. Area-wide statistical techniques designed to measure the degree to which cases may cluster in time and space have failed to document any consistent tendency, except perhaps in childhood cancers (*12–14*). If further knowledge is to develop in this difficult area of public health practice, it is among childhood cancers that work should focus (*15*).

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Infant Metabolic Alkalosis and Soy-Based Formula — United States

MMWR 1979;28:358–9 (August 3, 1979)

Three cases of a Bartter-like syndrome in infants were reported to CDC from Memphis, Tennessee, on July 26, 1979. The infants were less than 10 months of age and were failing to gain weight. They had poor appetites, and one had a history of constipation. All were hypochloremic and hypokalemic, with varying degrees of alkalosis and microhematuria. The 3 infants were taking the same brand of soy-based formula.

To further investigate this possible association, CDC surveyed a sample of pediatric nephrologists throughout the country for cases of metabolic alkalosis diagnosed since January 1, 1979, in infants with a history of failure to thrive, anorexia, or constipation. Infants known to have pyloric stenosis, cystic fibrosis, or diuretic therapy were excluded.

An additional 15 cases were ascertained through the survey, and another 16 cases were determined from other sources. Cases were scattered throughout the country. The infants ranged in age from 2 to 9 months; none died. There was no unusual sex distribution.

Feeding history was available in 27 of the 31 cases. Of these, 26 were on Neo-Mull-Soy (Syntex, Palo Alto, California), the same formula used by the 3 index cases. Neo-Mull-Soy represents 10%–12% of the soy-based formula market. After diagnosis of the alkalosis, infants who were placed on chloride supplement responded favorably; those who, after treatment for and recovery from the alkalosis, went back on the formula—but without chloride supplementation—had a recurrence.

The manufacturer of Neo-Mull-Soy has voluntarily stopped manufacturing this product, halted its distribution to wholesalers, and requested that wholesalers stop sales to retailers. Syntex has also issued a mailgram to pediatricians and pediatric residents notifying them of the problem.

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Editorial Note: Bartter syndrome is characterized by hypochloremic, hypokalemic alkalosis; normal blood pressure; and increased serum levels of renin and aldosterone. The onset is usually during the first year of life. The pathogenesis is not known.

The high percentage of affected infants on Neo-Mull-Soy formula and the fact that infants who were switched to other soy formulas did not have recurrence both support the casual association between Neo-Mull-Soy formula and this outbreak.

Insufficient intake of chloride is a known cause of metabolic alkalosis. The cause of this outbreak is not yet clear, but it is possible that the chloride concentration in this formula falls below the daily requirement for infants, if they are not also receiving chloride from other dietary sources. The current tendencies to delay the addition of solids to infants' diets and to remove sodium chloride from commercial and home-prepared baby foods might be additional contributing factors.

There are no regulations pertaining to the optimal level of chloride in infant formulas. The Committee on Nutrition of the American Academy of Pediatrics recommends a minimum of 11 milliequivalents per liter in infant formula (*1*).

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Editorial Note—1996

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At the time of this cluster of cases of hypochloremic metabolic alkalosis, infant formula was regulated under 21 CFR 105.65, *Infant Foods*. This regulation specified minimum levels of certain nutrients for infant formulas, including protein, fat, and some vitamins and minerals; a level for chloride was not specified. If the specified levels of nutrients were not present in the formula, the label was required to state that the diet should be supplemented. The incident described in this report prompted the Infant Formula Act of 1980*—the amendment of the federal Food, Drug, and Cosmetic Act that established a new section 412 (21 U.S.C. 350a) and created a separate category of food designated as infant formula. Section 412 requires that infant formulas meet specified standards of quality and safety and contain all required nutrients, including chloride, at specified levels. The Infant Formula Act of 1980 was the first in a series of major legislative and regulatory steps taken to ensure the safety of infant formulas† (*1,2*).

This episode underscores the need for regular and adequate testing of infant formulas. Several events may have contributed to the formula chloride deficiency, including removal of sodium chloride from the formula for the purpose of reducing the sodium content of infant diets. The cummulative effect of these contributing events led to a deficiency that was not recognized because regular testing for chloride content was not conducted.

In follow-up to the investigation in 1979, CDC established a registry of children who developed hypochloremic metabolic alkalosis following consumption of chloride-deficient Neo-Mull-Soy and Cho-Free, another soy-based formula manufactured by Syntex. Based on these data, the National Institutes of Health conducted a follow-up study to determine whether the risk for developmental delays or deficiencies was increased in these children (*3*). The study determined that by age 9–10 years, the children appeared to have recovered from their early growth failure and to have achieved normal cognitive development. However, these children remained at potential risk for deficits in language skills that require expressive language abilities (*3*).

*Public Law 96-359.
†Public Law 99-570.

This investigation highlights the critical importance of developing and using appropriate case definitions for surveillance and in investigations of outbreaks of both infectious and noninfectious origin. The original diagnosis of these cases was Bartter syndrome, a condition that causes metabolic alkalosis from renal loss of potassium and requires a large replacement dose of potassium chloride throughout life to maintain metabolic homeostasis. The children who had hypochloremic metabolic alkalosis as the result of consuming chloride-deficient formula quickly recovered following treatment with small doses of potassium chloride. This clinical response provided a clue to the physician who reported the first three cases that the formula might be the cause of the metabolic alkalosis. As a result, CDC's survey of pediatric nephrologists was used to search for cases of metabolic alkalosis resembling Bartter syndrome, rather than confirmed cases of that condition. If the case definition in this survey had been restricted to Bartter syndrome only, the association may not have been detected.

The outbreak described in this report highlights the value of a rapid response capability for local and state health departments and the Public Health Service and the important role played by clinicians in identifying public health emergencies. The sequence of problem recognition, investigation, and response unfolded rapidly: on July 26, 1979, CDC was notified of the three cases from Memphis and of the causal hypothesis related to infant formula as suggested by the attending physician. On July 27, two of CDC's Epidemic Intelligence Service (EIS) officers reported for their first day of work on assignment to CDC's Birth Defects Branch and assisted in developing a strategy for collecting information about feeding histories of children with metabolic alkalosis. On July 30, the nationwide survey of pediatric nephrologists was conducted. On August 1, one EIS officer traveled to the manufacturer's corporate headquarters to meet with company officials and three pediatricians. The company tested several formula batches before the meeting and found that none contained sufficient chloride. On August 2, after meeting with representatives of the Food and Drug Administration, the company halted manufacture of the formulas, initiated a voluntary recall of the products, and notified health-care professionals throughout the country about the problem. The *MMWR* article describing the occurrence was released to the news media that same day, only 7 days after CDC received notification of the first three cases from Memphis.

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Temporal Trends in the Incidence of Birth Defects — United States

MMWR 1979;28:401–2 (August 31, 1979)

Through CDC's Birth Defects Monitoring Program (BDMP), a total of 161 categories of birth defects are analyzed quarterly to determine increases or other unusual trends. Sixteen of these malformations have been selected for review in this report because they occur in sufficient numbers to provide relatively stable rates, the coding categories for them are relatively homogenous, and they represent defects of different organ systems.

Data on the incidence of these 16 malformations in the United States in 1970-1971 and in 1976-1977 were compared, and the geometric mean percentage change in rates that occurred in the 6-year interval between these periods was calculated (Table 1). Six malformations changed an average of 5% or more per year. Anencephaly and spina bifida—2 of the most common, serious, and easily diagnosable defects—decreased 5.4% and 6.7% per year, respectively (Figure 1). The cause of this decrease is unknown.

The reported incidence of ventricular septal defect doubled, and that for patent ductus arteriosus tripled (Figure 1). A substantial search for the cause of these increases was done in the greater Atlanta area, but it could not be determined whether these increases were due to biologic factors or reporting methods (*1,2*).

The incidence of congenital hip dislocation (without central nervous system anomalies) increased an average of almost 25% per year. Part of the increase was artifactual: a coding change in 1974 assigned hip dysplasia to the hip dislocation category. In addition, the diagnosis of this defect lacks clear, reproducible criteria. Changes in the manner of newborn examinations can, therefore, make substantial changes in reported incidence.

The reported incidence rate of renal agenesis increased an average of 9.7% per year. This increase—as yet unexplained—is under investigation.

Reported by Birth Defects Br, Chronic Diseases Div, Bur of Epidemiology, CDC.

Editorial Note: The BDMP is conducted by CDC's Birth Defects Branch with data provided under contract by the Commission on Professional and Hospital Activities (CPHA) in Ann Arbor, Michigan. BDMP's primary purpose is to monitor the incidence of birth defects and other newborn conditions. Abstracts of hospital discharge summaries are coded by medical records staff from participating hospitals and submitted regularly to CPHA for data processing. CPHA uses some of the data on newborns to produce monitoring reports and other tabulations; these are sent to CDC for analysis. Since 1970, the tabulations have covered the births of 8 million infants. The present annual number of births covered, from 1,130 hospitals, is 975,000—about one-third of the births in the country.

The advent of new means for the prevention of birth defects or of a widespread exposure to a powerful new teratogen would likely be followed by substantial changes in the incidence of birth defects. Rh hemolytic disease, for example, decreased following the widespread availability and use of rhesus immune globulin (RhIG) (*3*). In the period covered in this report, the incidence of the majority of birth defects neither substantially decreased nor increased. The paucity of decreasing rates indicates the need for discovering and implementing prevention strategies for birth

TABLE 1. Incidence of selected malformations reported to the Birth Defects Monitoring Program, 1970-1971 and 1976-1977

Malformation	Cases		Rates*		Mean annual percent change
	1970-1971	1976-1977	1970-1971	1976-1977	
Anencephaly	949	833	5.48	3.94	– 5.4
Spina bifida without anencephaly	1,306	1,053	7.55	4.97	– 6.7
Hydrocephalus without spina bifida	833	925	4.81	4.37	– 1.6
Transposition of great vessels	131	175	0.76	0.83	+ 1.5
Ventricular septal defect	770	1,889	4.45	8.92	+12.3
Patent ductus arteriosus	686	2,804	3.96	13.25	+22.3
Cleft palate without cleft lip	873	1,093	5.05	5.16	+ 0.4
Cleft lip with or without cleft palate	1,715	1,890	9.91	8.93	– 1.7
Clubfoot without CNS† defects	4,756	4,912	27.49	23.21	– 2.8
Reduction deformity	547	705	3.16	3.33	+ 0.9
Hip dislocation without CNS defects	1,382	6,407	7.99	30.27	+24.9
Tracheo-esophageal fistula	289	327	1.67	1.54	– 1.3
Rectal atresia and stenosis	648	679	3.75	3.21	– 2.6
Renal agenesis	123	263	0.71	1.24	+ 9.7
Hypospadias	3,565	5,036	40.02‡	46.22‡	+ 2.4
Down's syndrome	1,413	1,590	8.17	7.51	– 1.4

*Cases per 10,000 total births.
†Central nervous system.
‡Cases per 10,000 male births.

defects—the cause of nearly 20% of infant mortality in the United States. The paucity of increases suggests that few, if any, widespread and powerful new teratogens were introduced. The possibility of such an introduction requires continuing surveillance of the incidence of birth defects in the United States.

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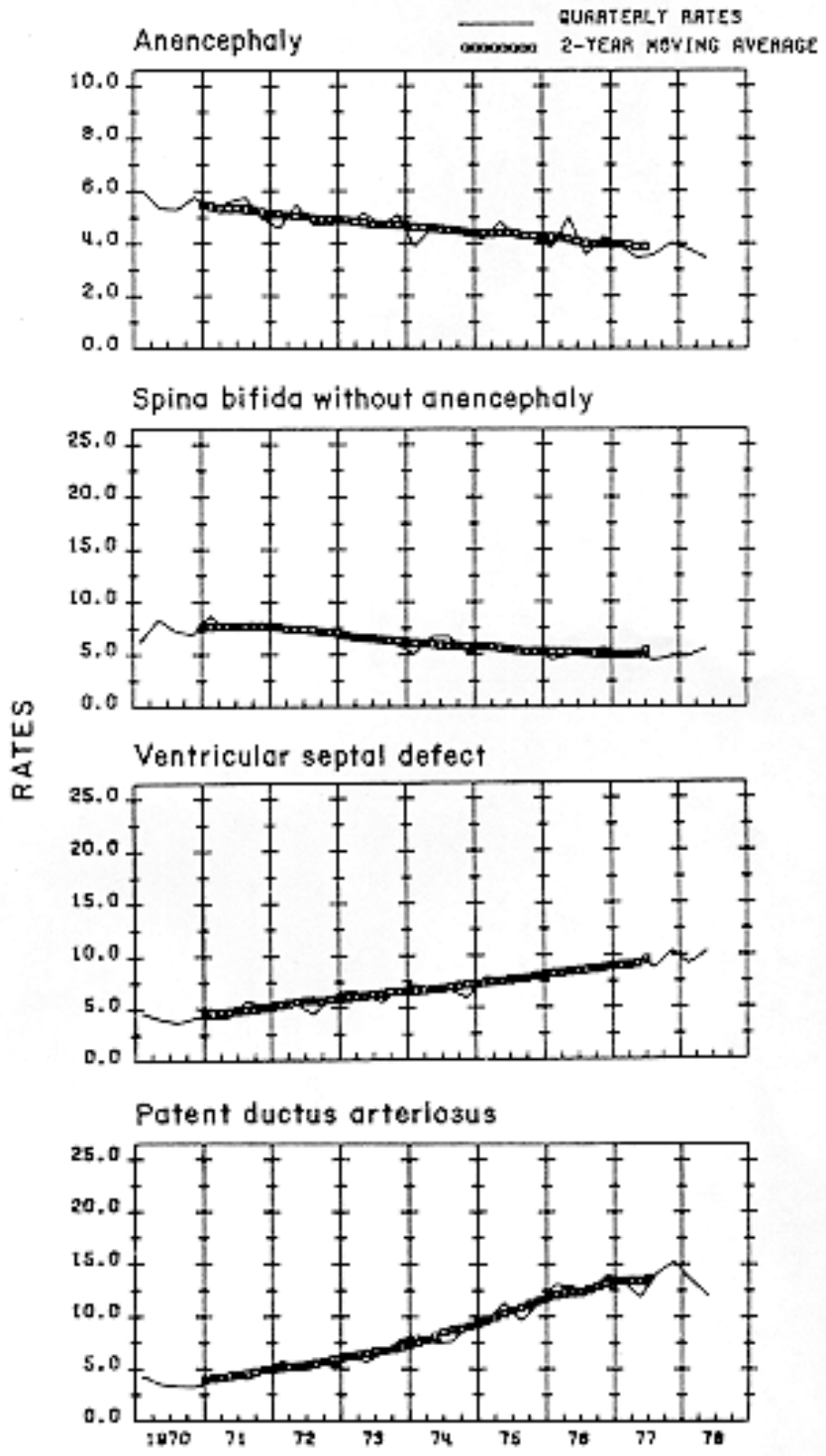
FIGURE 1. Trends in reported incidence* of 4 birth defects reported to the Birth Defects Monitoring Program, by quarter of birth, January 1970 through June 1978



*Rates per 10,000 total births.

Editorial Note—1997

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Birth defects are the leading cause of infant mortality in the United States (*1,2*), and 18 of the most common birth defects account for annual expenditures of $8 billion (*2*). Even though the prevention of birth defects improves the health of children, prevention efforts have been hampered because the specific causes of most (75%) are unknown. CDC's involvement in the surveillance for birth defects began in late 1967 when Clark Heath, M.D., Chief of the Leukemia Section, Viral Diseases Branch, Epidemiology Program, and Epidemic Intelligence Service Officer Allan Ebbin, M.D., with the support of CDC Chief Epidemiologist Alexander Langmuir, M.D., and Arthur Falek, M.D., and Suzanne Schimpler of the Georgia Mental Health Institute, established birth defects surveillance in metropolitan Atlanta (*3*). This local surveillance program provided not only excellent surveillance data but also the foundation on which CDC built a group of public health scientists dedicated to determining the causes of birth defects and to preventing birth defects.

One purpose of birth defects surveillance is to provide an early warning of an "emerging" birth defects problem. Moreover, an important rationale for birth defects surveillance is that appropriate surveillance programs might have enabled more rapid identification of the birth defects associated with maternal use of thalidomide in Europe during the late 1950s and early 1960s and, thereby, might have contributed to a more timely ending of that tragic epidemic. However, subsequent epidemics of birth defects cannot be predicted, and a single local surveillance system, while providing useful information about exposures that are distributed relatively equally throughout the country, cannot provide data about other regions. For these reasons, in the early 1970s, Virginia Apgar, M.D., and her colleagues at the March of Dimes/Birth Defects Foundation articulated the need for a national birth defects surveillance system. After discussions with Dr. Apgar and her colleagues, CDC's William Flynt, M.D., with funding from the National Institute for Child Health and Human Development, established the national BDMP in 1973 (*4*).

In the August 31, 1979, issue of *MMWR*, BDMP rates for 16 birth defects during 1970–1971 were compared with those during 1976–1977; the results indicated that the reported rates for most birth defects were stable, although rates for some were either increasing or decreasing. These findings indicated that the epidemiologies of various birth defects can be as different as the varying epidemiologies of different infectious diseases. The figure presented in the 1979 *MMWR* showed declines in the rates of spina bifida and anencephaly—two common and severe birth defects with many similar epidemiologic findings. These declines were consistent with improvement in the environment (e.g., improved nutrition and fewer exposures to harmful chemicals).

During the weeks surrounding publication of the 1979 *MMWR*, CDC staff members learned of a study in England suggesting that one or more vitamins might prevent spina bifida and anencephaly (*5*). At the same time, CDC's David Erickson, D.D.S., and colleagues were designing the Atlanta birth defects case-control study to assess the increased risk for birth defects among children of Vietnam veterans (*6*); the design included questions about the mothers' use of vitamins before and during the early weeks of pregnancy. Findings of this study included a strong association between

regular maternal consumption of multivitamins before and during early pregnancy and a reduction in risk for having a child with spina bifida and/or anencephaly (*7*).

In 1991, the results of a randomized clinical trial from the United Kingdom established that folic acid was the specific vitamin associated with prevention of spina bifida and anencephaly (*8*). Following publication of those results, the CDC birth defects group assisted in fostering a science-based public policy for this "emerged" prevention opportunity. In particular, CDC guidelines for high-risk women (i.e., those with a previous spina bifida- or anencephaly-affected pregnancy) were published in *MMWR* 2 weeks after the publication of the randomized clinical trial (*9*). Findings of earlier case-control studies (*7*) supported the Public Health Service (PHS) recommendation published September 11, 1992, that all women of reproductive age consume 400 μg of folic acid each day to prevent neural tube defects (*10*). In the United States, these two recommendations have served as the foundation for intervention programs subsequently implemented by industry, public health organizations, and voluntary agencies (e.g., the March of Dimes Birth Defects Foundation and the Spina Bifida Association of America). In 1996, the Food and Drug Administration issued regulations that required "enriched" cereal-grain products to be fortified with folic acid no later than January 1, 1998 (*11*). As a result of this fortification, the consumption of folic acid by U.S. women will increase by 100 μg per day.

Birth defects surveillance data are important in evaluating the effectiveness of prevention programs. The BDMP was discontinued during the mid-1990s because of changing technology, but was replaced by a network of state-based surveillance systems. In 1992, Congress mandated that CDC establish such a network to collect, analyze, and share data needed to prevent birth defects. By 1996, CDC assistance to states had included the establishment of the National Birth Defects Prevention Network (NBDPN), with a mission of creating and maintaining a national network of state- and population-based programs for birth defects surveillance and research. These programs assess the impact of birth defects on children and families; identify factors that can be used to develop primary prevention strategies; and assist families and their health-care providers in secondary prevention of disabilities. NBDPN recently reported on data from 21 states (*12*). These surveillance systems will be used to assist health officials in assessing efforts to prevent folic acid-preventable birth defects and in providing surveillance data for etiologic research.

State-based birth defects surveillance systems have not yet detected changes in the rates of spina bifida and anencephaly. Conversely, surveys of folic acid consumption indicate that approximately 45 million women of reproductive age still do not consume sufficient folic acid to protect the children they may have from neural tube defects (*13*). During the next 10 years, additional programs to increase the amount of folic acid consumed by women of reproductive age could result in the prevention of most folic-acid preventable spina bifida.

In 1996, CDC intensified efforts to prevent birth defects by establishing a new program comprising eight Centers for Birth Defects Research and Prevention (CBDRP). These eight centers collaborate in epidemiologic studies to provide a timely, continuing source of information on potential causes of birth defects. Each center also will maintain center-specific, investigator-initiated research projects. This new program should assist in advancing the prevention of birth defects by identifying modifiable

causes of birth defects, just as earlier epidemiologic studies identified folic acid as the agent that can prevent serious birth defects in thousands of children each year.

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Smoking-Attributable Mortality and Years of Potential Life Lost — United States, 1984

MMWR 1987;36:693–7 (October 30, 1987)

Cigarette smoking has been identified as the chief avoidable cause of death in the United States (*1*). Several estimates of mortality attributable to cigarette smoking have been reported, including 270,000 deaths for 1980 (*2*) and 314,000 deaths for 1982 (*3*). Published estimates vary considerably because of changing mortality rates, decreasing smoking rates, and differences in methods used. Smoking-attributable mortality and years of potential life lost (YPLL) for 1984 are analyzed in this report.

Relative risk (RR) estimates for smoking-related diseases and prevalence estimates of current, former, and never smokers among adults ≥20 years of age were used to calculate the smoking-attributable fraction (SAF) and smoking-attributable mortality for 19 underlying causes of death (*2*) (Table 1).* Age-, sex-, and race-specific mortality data for 1984 were obtained from National Center for Health Statistics reports. Age-, sex-, and race-specific smoking prevalence rates were obtained from the 1985 Current Population Survey (Supplement) of the Bureau of the Census (Office on Smoking and Health, CDC, unpublished data). Years of potential life lost were calculated to age 65 according to previously described methods (*6*). Age-adjusted smoking-attributable mortality and YPLL rates were calculated by the direct method, with the 1984 U.S. population used as the standard.

For deaths among adults, the disease-specific SAFs are derived from RR estimates for current and former smokers that are weighted averages from four prospective studies (*7–10*). RR estimates for women based on these studies may be lower than the current RRs for many of the specific smoking-related diseases among women. However, the SAF for lung cancer among women (0.75) has been updated based on RR estimates from more recent mortality data (*11*). Race-specific RR estimates for smoking-attributable diseases were not available.

For four pediatric diagnoses, the mortality attributed to maternal smoking during pregnancy for children <1 year of age was determined. These calculations used RR estimates from McIntosh (*12*) and current smoking prevalence among women 20–64 years of age as a proxy for the percentage of pregnant women who smoke. The RR (1.50) for sudden infant death syndrome from McIntosh (*12*) was used, but the RR (1.76) for total infant mortality reported by McIntosh was used to calculate the SAF for only three specific infant death categories (short gestation/low birthweight, respiratory distress syndrome, and other respiratory conditions).

An estimated 315,120 deaths and 949,924 YPLL before age 65 years resulted from cigarette smoking in 1984 (Table 2). The smoking-attributable mortality rate among men is more than twice the rate among women, and the rate among blacks is 20% higher than the rate among whites (Table 3). The smoking-attributable YPLL rate

*The equation for calculating the smoking-attributable fraction of each disease category is: $SAF=[p_0 + p_1(RR_1) + p_2(RR_2)] - 1/[p_0 + p_1(RR_1) + p_2(RR_2)]$ where p_0=percentage of never smokers, p_1=percentage of current smokers, p_2=percentage of former smokers, RR_1=relative risk for current smokers (relative to never smokers), and RR_2=relative risk for former smokers (relative to never smokers) (*4*). This formula is derived from the standard attributable risk (AR) formula (*5*): $AR=p(RR - 1)/[p(RR - 1) + 1]$.

among men is more than twice the rate among women, and the rate among blacks is more than twice the rate among whites (Table 3).

Reported by: Office on Smoking and Health, Center for Health Promotion and Education, CDC.

Editorial Note: The total smoking-attributable mortality and YPLL reported here is similar to that cited in previous reports (*2,3*), showing that the disease impact of

TABLE 1. Total mortality, weighted smoking-attributable fractions (SAF), and smoking-attributable mortality (SAM), by disease category and sex — United States, 1984

Disease Category*		Males			Females			Total SAM†
		Deaths	SAF	SAM	Deaths	SAF	SAM	
Adults ≥20 years old								
Neoplasms:								
140-149	Lip, oral cavity, pharynx	5,754	0.688	3,958	2,689	0.413	1,110	5,068
150	Esophagus	6,310	0.589	3,717	2,345	0.536	1,257	4,974
151	Stomach	8,468	0.172	1,455	5,772	0.254	1,467	2,922
157	Pancreas	11,513	0.300	3,459	11,634	0.142	1,653	5,112
161	Larynx	2,959	0.806	2,385	664	0.413	274	2,660
162	Trachea, lung, bronchus	82,459	0.796	65,659	36,227	0.750	27,170	92,829
180	Cervix uteri	0	0.0	0	4,562	0.369	1,685	1,685
188	Urinary bladder	6,597	0.371	2,447	3,114	0.274	853	3,299
189	Kidney, other urinary	5,424	0.243	1,319	3,403	0.118	403	1,722
Circulatory diseases:								
401-405	Hypertension	13,464	0.156	2,099	17,855	0.148	2,645	4,744
410-414	Ischemic heart disease <age 65	78,340	0.285	22,362	27,000	0.181	4,892	27,253
410-414	Ischemic heart disease ≥age 65	211,003	0.159	33,461	224,756	0.075	16,816	50,276
427.5	Cardiac arrest	19,392	0.399	7,745	17,296	0.344	5,950	13,695
430-438	Cerebrovascular disease	59,185	0.096	5,692	88,285	0.139	12,228	17,920
440	Arteriosclerosis	9,235	0.238	2,200	15,216	0.315	4,797	6,996
441	Aortic aneurysm	10,323	0.624	6,444	4,791	0.468	2,244	8,689
Respiratory Diseases:								
480-487	Pneumonia, influenza	28,774	0.208	5,986	28,935	0.093	2,679	8,664
491-492	Chronic bronchitis, emphysema	10,708	0.850	9,097	5,517	0.694	3,831	12,928
496	Chronic airways obstruction	31,240	0.850	26,541	16,625	0.694	11,545	38,085
Digestive diseases:								
531-534	Ulcers	3,251	0.479	1,556	3,365	0.445	1,497	3,053
Pediatric diseases, <1 year old								
765	Short gestation, low birthweight	1,729	0.182	314	33	0.182	279	593
769	Respiratory distress syndrome	2,178	0.182	396	1,379	0.182	251	647
770	Other respiratory conditions of newborn	1,982	0.182	360	1,515	0.182	275	636
798.0	Sudden infant death syndrome	3,176	0.128	405	2,069	0.128	264	669
Total†				**209,057**			**106,063**	**315,120**

* *International Classification of Diseases, Ninth Revision.*
† Sums may not equal total because of rounding.

TABLE 2. Estimated smoking-attributable mortality and years of potential life lost (YPLL)*, by race and sex — United States, 1984

	Mortality			YPLL		
	Males	**Females**	**Total†**	**Males**	**Females**	**Total†**
Whites	184,296	95,340	279,636	489,827	199,590	689,418
Blacks	22,647	10,131	32,779	129,952	63,473	193,425
Total population§	**209,057**	**106,063**	**315,120**	**661,651**	**288,273**	**949,924**

*YPLL before age 65.
†Sums may not equal total because of rounding.
§Includes whites, blacks, and racial category "other."

TABLE 3. Age-adjusted smoking-attributable mortality rates* and years of potential life lost (YPLL) rates†, by race and sex — United States, 1984

	Mortality rate			YPLL		
	Males	**Females**	**Total†**	**Males**	**Females**	**Total**
Whites	189.7	64.2	119.0	5.56	2.17	3.81
Blacks	236.5	75.5	143.2	12.07	4.85	8.14
Total population§	**192.6**	**68.0**	**133.2**	**6.53**	**2.71**	**4.56**

*Per 100,000 persons (population data from 1984 U.S. Census).
†YPLL before age 65/1,000 persons <65 years (population data from 1984 U.S. Census).
§Includes whites, blacks, and racial category "other."

smoking in the United States continues to be enormous despite recent declines in the prevalence of smoking. These figures do not include mortality and YPLL due to peripheral vascular disease (for which specific RR estimates are generally lacking), cancer at unspecified sites, cigarette-caused fires, or involuntary (passive) smoking. In 1984, an estimated 1,570 deaths were attributed to cigarette-initiated fires (*13*); an estimated 3,825 nonsmokers per year die from lung cancer attributed to involuntary smoking (*14*). When the figures for fires and involuntary smoking are included, the estimated total of smoking-attributable deaths in the United States in 1984 is 320,515, or 15.7% of all (2,039,369) U.S. deaths. Total smoking-attributable YPLL (949,924) represents 8.1% of all (11,761,000) U.S. YPLL before age 65 (excluding YPLL due to cigarette-caused fires or involuntary smoking).

Among blacks, the smoking-attributable mortality (32,779) represents 13.9% of total 1984 mortality (235,884), whereas the smoking-attributable mortality for whites (279,636) was 15.7% of total 1984 mortality (1,781,897), excluding deaths due to fires or involuntary smoking. However, the smoking-attributable mortality rate and YPLL rate were higher among blacks than among whites. These differences in rates reflect a higher prevalence of smoking and a higher mortality rate from smoking-related diseases among blacks. Higher YPLL rates among blacks may also reflect more smoking-attributable deaths at earlier ages. Because blacks tend to smoke fewer cigarettes per day than whites (*15,16*), the difference in smoking-attributable mortality and YPLL rates between blacks and whites may be slightly overestimated. On the other hand, the RR of smoking-related diseases among blacks may be higher than the RR estimates used here because of increased interactions between smoking and other risk

factors, different tar and nicotine exposures, or different smoking patterns. Still, these findings support previously cited concerns regarding the increased burden of smoking-related disease among blacks (*17*).

Smoking prevalence for 1985 was used to calculate the SAFs in this study. However, the 1984 smoking-related mortality is a result of a higher smoking prevalence during the 1950s, '60s, and '70s, the decades during which these diseases were developing. Therefore, the SAFs used here are conservative.

CDC has examined YPLL before age 65 years since 1979 (*6*). In this study, most smoking-related deaths (218,691, or 69.4%) occurred among persons ≥65 years of age. Thus, the smoking-attributable YPLL among persons <65 reported here (949,924) is substantially lower than the 3.6 million smoking-attributable YPLL calculated when the average life expectancy in the United States is used for calculating YPLL for 1984.

Group-specific calculations such as these are possible for states and other defined populations if mortality and smoking prevalence data for those populations are available. A computer program has recently been developed to aid in calculating mortality and YPLL attributed to cigarette smoking (*18*). CDC is now collaborating with all 50 state health departments, Puerto Rico, and the District of Columbia to perform similar studies. Results from this project will be reported in 1988.

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Editorial Note—1997

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In 1987, CDC published the preceding report that provided a detailed and comprehensive estimate of the number of deaths attributed to cigarette smoking in the United States. Using the attributable fraction, which measures the magnitude of a public health problem accounted for by an etiologic agent, CDC was able to quantify the impact of smoking. This method established that smoking was the leading cause of preventable deaths in the United States (*1*). As a result, increased emphasis was placed on decreasing the health burden caused by tobacco use and on reducing cigarette smoking. Since this SAM estimate was published in 1987, continued research has increased understanding of the health risks associated with tobacco use, including nicotine addiction and the recognition that addiction begins in childhood. Public health programs have responded by focusing on preventing tobacco use among adolescents, assisting in tobacco-use cessation, and protecting nonsmokers from environmental tobacco smoke. This contemporary editorial note reviews previous SAM estimates, presents new SAM estimates for 1990–1994, and discusses future implications.

SAM and YPLL estimates for the United States published since the first estimate for 1984 include 390,000 deaths for 1985, 434,000 deaths and 6 million YPLL before age 85 for 1988, and 418,000 deaths and 5 million YPLL to life expectancy for 1990 (*2*). SAM and YPLL also have been estimated for all 50 states and the District of Columbia for 1985 and for 1990 (*3*). Although all estimates were calculated by the same equation used for the SAF, the data sources, study populations, and causes of death have changed. The Smoking-Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) software program has also been used for calculating these estimates (*2*).

Since 1989, RR estimates for calculating SAM and YPLL have been obtained from the American Cancer Society's Cancer Prevention Study II (CPS-II) for 1982–1986 (*4*). The CPS-II was selected, in part, because it is the largest prospective U.S. study that has collected data on the relation between smoking and mortality (*4*). Recent SAM estimates for adults have been limited to persons aged ≥35 years because the CPS-II study population was restricted to this age range. Deaths from stomach cancer and ulcers were dropped from the calculation of SAM because a causal relation has not been established (*4*). Conversely, the cardiovascular and respiratory disease categories were expanded to include the *International Classification of Diseases, Ninth Revision* [ICD-9], codes 390–398, 415–417, 420–429, 442–448, 010–012, and 493. The CPS-II data also enabled the calculation of the RR for smoking and cerebrovascular disease, which declines with age (*4*), for two age groups (35–64 years and ≥65 years).

Cigarette smoking remains the leading preventable cause of death in the United States. The same methods and data sources that were used to calculate the 1990 SAM and YPLL (*2*)[†] were used for the 1990–1994 calculations, which indicated that 2,153,700 deaths (1,393,200 men and 760,400 women; total annual average: 430,700 deaths) were attributed to smoking (19.5% of all deaths). A total of 906,600 of these deaths resulted from cardiovascular diseases; 778,700, from neoplasms; 454,800, from nonmalignant respiratory diseases; 7900, from diseases among infants; and 5500, from smoking-related fires. Lung cancer (616,800 deaths), ischemic heart disease (IHD) (490,000 deaths), and chronic airway obstruction (270,100 deaths) accounted for most deaths. During 1990–1994, cigarette smoking resulted in 5,732,900 YPLL before age 65 years and in 28,606,000 YPLL to life expectancy.

During 1990–1994, estimates of SAM were higher among men than among women, reflecting their longer duration and higher prevalence of smoking and greater numbers of cigarettes smoked per day (*6*). Annual SAM rates will probably remain stable if current trends in smoking prevalence among adults continue. Although the prevalence of smoking among persons aged ≥35 years decreased from 1985 to 1990 (28.4% to 24.1%), during 1990–1994, smoking prevalence remained relatively constant—at 23.6%–24.8% (CDC, unpublished data). However, the prevalence of smoking among U.S. adolescents has been increasing since 1992 (*7*). If these smoking patterns continue into adulthood, SAM and YPLL are expected to increase. Assuming that one third of adult smokers, 10% of former smokers, and 5.3 million persons aged <18 years die from smoking and that current smoking patterns continue, an estimated 25 million persons alive today will die prematurely from smoking-related illnesses (*7,8*).

Lung cancer has been and probably will continue to be the leading cause of SAM because, although lung cancer death rates are decreasing among men, rates are continuing to increase among women (*9*). Among women, death rates for lung cancer have surpassed those for breast cancer since 1987 (*9*). In addition, because recent trends indicate a slowing of the decline in IHD mortality, IHD will probably remain a major contributor to SAM (*9*).

SAM and YPLL may be underestimated for several reasons (*2*); recent studies have addressed two of these reasons. First, SAM and YPLL estimates are based on the prevalence of current and former smokers in the current year; however, the deaths that occur during a given year are primarily among persons who began smoking 30–50 years earlier (*10*), many of whom have quit smoking (*10*). Including these persons in the prevalence estimates of former smokers may decrease the SAF because the summary measure of risk for former smokers does not reflect their increased likelihood of dying from a smoking-related disease (*4*). Among whites, expanding the classification of smoking to include information on duration and number of cigarettes smoked per day resulted in 10% larger SAM estimates for IHD than SAM estimates in which smoking was categorized as current, former, and never (*10*). Second, the SAM estimates do not include mortality caused by cigar smoking, pipe smoking, or smokeless tobacco use. Approximately 1000 deaths were attributable to pipe smoking in 1991 (*11*).

[†]Except for the prevalence of smoking among pregnant women in the United States for 1992 through 1994, which was estimated from the 1992–1993 National Pregnancy and Health Survey (*5*).

Although SAM and YPLL estimates are not adjusted for confounders (*2–4*), a recent study has documented little change in SAM estimates after adjustment for confounders (*12*). Among whites, SAM estimates for the combined disease categories of lung cancer, IHD, bronchitis/emphysema, chronic airway obstruction, and cerebrovascular disease were 2% higher than age-adjusted estimates after adjustment for relevant confounders including age, education, alcohol intake, diabetes, and hypertension (*12*).

Cigarette smoking has resulted in approximately 10 million deaths since the first Surgeon General's report on smoking and health in 1964 (*2,4,13*). In 1993, $50 billion in medical costs were attributable to smoking (*14*). The human and economic costs of smoking will continue to accumulate until the completely effective implementation of public health efforts to prevent initiation, to promote cessation, and to protect nonsmokers from the adverse effects of environmental tobacco smoke. Examples of such efforts include Food and Drug Administration regulations to restrict youth access to tobacco and to reduce the appeal of cigarette advertising to youth (*7*); comprehensive state-based efforts, including tax increases and earmarked funding for tobacco-use prevention and mass media campaigns similar to those in Massachusetts and California (*15*); physician adherence to the Agency for Health Care Policy and Research's smoking cessation guidelines (*8*); institutional adoption of the Guidelines for School Health Programs to Prevent Tobacco Use and Addiction (*16*); and clean indoor-air policies that protect nonsmokers.

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