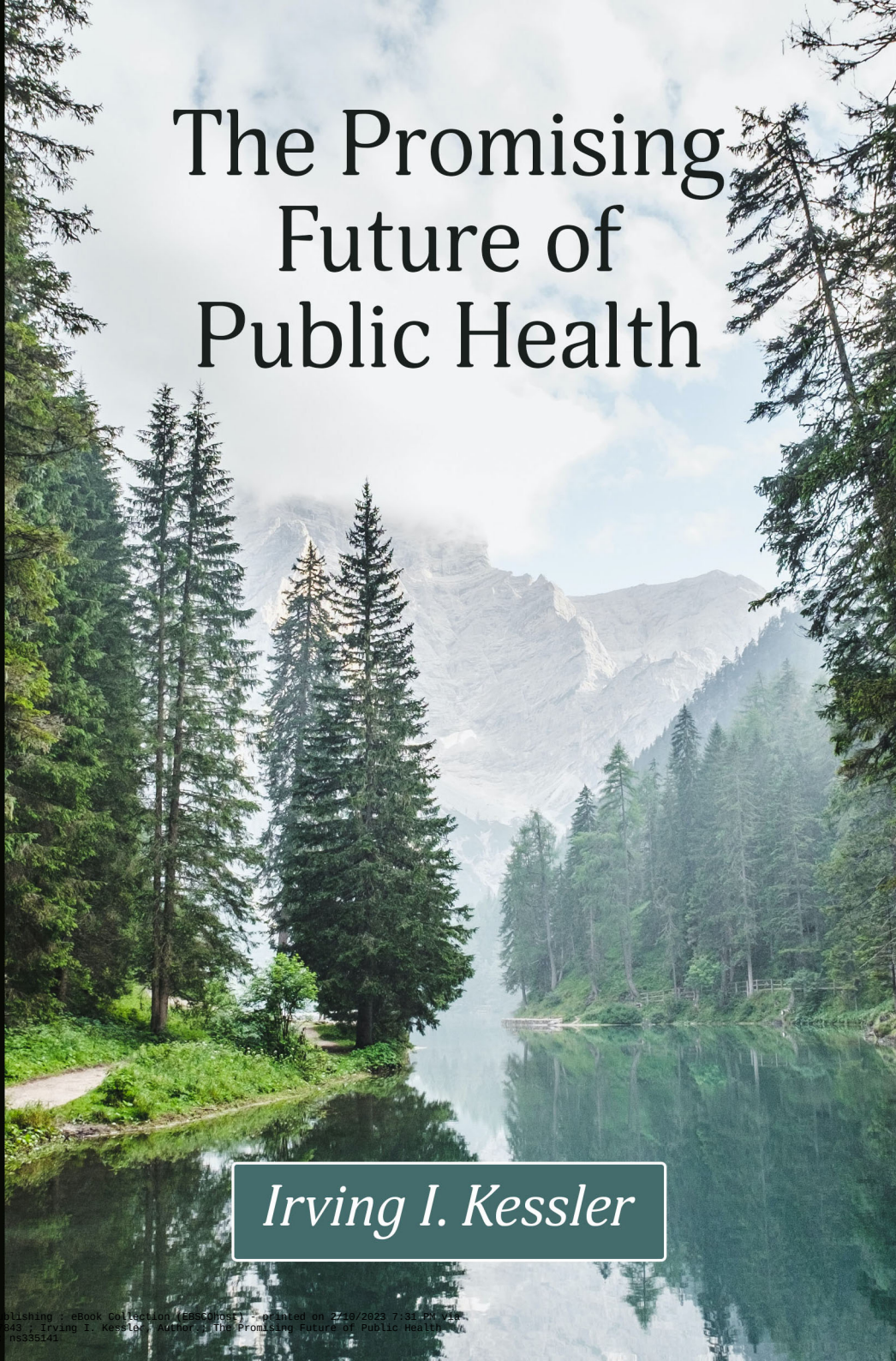

The Promising Future of Public Health

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By

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All my love to Laure, Stella, Ari, Amalia and Adam
for nurturing our family ties.

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PREFACE

As it evolved over time, medicine was primarily concerned with public health. The famous physicians of antiquity prescribed foods, habits, exposures, sins, and divinities as the critical agencies of health and disease. Their recommendations usually ended after the demise of a nation's leader, though some became permanent fixtures in the culture of certain societies. Kashrut, the ancient religious laws of Judaism, governed the diet, circumcision, quarantine, and personal hygiene regulations of the Israelites for thousands of years, while the vegetarian preferences of Hindus, Jains, and Buddhists are maintained to this very day.

Clinical medicine for individual patients slowly emerged during the past few centuries, as epidemiologically alert physicians began to notice diseases arising in patients eating certain foods or otherwise exposed to substances or conditions proven to be harmful through periodic observations of family members, the community, or the era's medicine men. When a sufficient number of consistent observations had been assembled, they became part of the records, teachings, and clinical practices of the time. In this fashion, the medical schools began to recognize etiologic factors of disease, which were disseminated throughout Europe and beyond. Since the mid-1800s, medical research has developed rapidly, as investigators and then comprehensive research institutes probed disease epidemics, began to understand the functions and malfunctions of human health and disease, and devised a myriad of techniques to detect their risk factors.

Early in this era, the anatomy and physiology of human beings, as well as their functions and malfunctions, were the principal subjects of concern. But, as investigators with PhD degrees in basic medical science multiplied, animal-based studies became the dominant experimental model, as the relative simplicity and lower cost of laboratory animal investigations outweighed all other considerations. Whether the animal species chosen for the study of a specific human disease was sufficiently homologous to Homo sapiens to justify its use was sometimes, but not invariably, considered.

Since then, physicians with epidemiological skills became the biomedical researchers undertaking the relatively complex human studies to test hypothesized risk factors for given diseases. The majority of such physicians, including myself, were associated with public health schools and preventive medicine departments in medical schools. But, over the past 30 years or so, the ground under their feet has been disrupted. Public health and medical schools have essentially eliminated entrance requirements for master and PhD degrees, so that the majority of matriculants in their programs are now seriously lacking knowledge of human health and disease, as well as the basic medical sciences. A small minority has been trained to undertake classical epidemiologic studies in humans, but most researchers now utilize computers with Big Data capabilities that make the critical analytical decisions for them. Graduates of public health programs these days generally end up in office jobs of government agencies, and would be unprepared to participate meaningfully in the design, conduct, or analysis of epidemiologically based human studies.

The urgency of publishing this volume is intensified because public health schools are now being established on college campuses remote from any medical school or hospital,

strongly suggesting that, in the minds of many, public health need no longer continue as a significant branch of medicine. Epidemiological reasoning and research on human disease will be permanently impaired if this view gains wider support.

This book is not a standard textbook on public health, of which many have been published. Rather, it is designed to offer the reader a multidisciplinary view of epidemiology and the diverse fields of public health and medicine in which it can be applied. Chapter 1 describes the development of medicine from its faith-based origins to modern science. This is followed by a detailed discussion in Chapter 2 of the flowering of epidemiology as the fundamental process of applying scientific reasoning to clinical observations in human biomedical research.

Sixteen studies conducted by the author while at Harvard, Johns Hopkins, and the University of Maryland Schools of Medicine and Public Health are presented next. These demonstrate the wide diversity of investigations in disease that are possible using traditional epidemiological methodologies, as well as other ventures designed to assist physicians in their clinical practice. Chapters 3 to 9 were undertaken during what many regard as a ‘Golden Age of Medicine and Public Health,’ a period when thousands of papers were published, in which researchers carefully reviewed the existing literature on human disease, proposed specific risk factors in living subjects, and critically discussed the results of the study. These efforts were largely completed during the earlier years of this era, when government regulations were modest and risk factor investigations as potential causes of human disease were plentiful. The reader should glean from these chapters a fuller understanding of the epidemiological relationships between clinical diseases and

their putative risk factors, as well as the captivating spirit of engaging in such endeavors.

Chapter 10 describes our Department of Public Health at the University of Maryland developing a uniquely rapid-reporting statewide cancer registry system while Chapter 11 focuses on our innovative training program in medical informatics to prepare the faculty and students for exploiting the enhanced capabilities of modern computing. The classic epidemiological approach to the COVID-19 pandemic is addressed in Chapter 12, an objective comparison of the costs and quality of medical care by dermatologists and family physicians is fully described in Chapter 13 and the details concerning our automated clinical information system for physicians in practice are presented in Chapter 14. These studies were developed during a later period when government regulations were maximal, epidemiological studies in humans had declined, and public health schools were emphasizing ancillary subjects rather than the pathogenesis of human disease. My duties as department chairman had greatly increased so that I proceeded with a multiplicity of projects without much concern for immediate publication. The readers of this section will come to better understand how well designed epidemiological investigations can address many of the long-ignored conundrums in public health and medicine. Such an array of data has never, to our knowledge, been made available to the medical community and the general public.

After detailing the many contributions of epidemiological reasoning in human studies of disease, the book concludes with Chapter 19 entitled “Assuring a Promising Future for Public Health.” It is here that the urgent need to reconfigure the public health education of physicians and nurses is emphasized. By having the medical and public health schools

add a graduate-level, degree-granting, and autonomous Clinical Public Health (CPH) department for physicians and nurses with a strong background in clinical medicine, such departments could eventually become each school's center for clinically oriented teaching and research on human disease. The CPH departments would become the primary pathway to prepare physicians and registered nurses for leadership roles in public health education, clinical practice, and epidemiology-based research on human disease.

It is essential that the CPH departments be physically separate from the ancillary departments that cater to the needs of students lacking a clinical or health background. All students desiring to expand their knowledge of health economics, healthcare policy, environmental health, hospital administration, genetics, and other ancillary subjects can attend such lectures, but the core courses on agent/host/environment epidemiology and human disease must be based in the CPH department, and the bulk of the students' time each day should be spent in the company of CPH faculty and students. This intense exposure to colleagues and faculty engaged in public health education and research will enrich the program immensely and benefit all participants.

After decades of relatively low productivity, the medical and public health schools will once again regain their leadership in public health, emboldened to resume their unique roles in advancing knowledge and training for public health practitioners to the benefit of mankind. The world at large will rejoice to see hundreds of young physicians and nurses attracted each year to programs designed to prepare them for careers in public health education, practice, and research on the causes of human disease, disability, and prevention.

Chapter 19 concludes with an outline of the steps necessary to establish CPH departments, including unique educational programs to assure their success, both academic and financial. Included in the chapter is a sampling of notable ventures that differ greatly from traditional offerings of Public Health Departments, and which will contribute substantially to the program's educational and financial viability.

I am very grateful to a number of my colleagues, including former students and academic colleagues who were among the pioneers of their generation in public health, and who agreed to read or comment on the book. Included in this number are: Prof. Rainer Frentzel-Beyme, MD MHS, University of Bremen; Prof. Joseph W. Burnett, MD, University of Maryland; Prof. Manning Feinlieb, MD, DrPH, NHLBI; Prof. Arnold Krieger, PhD, University of Maryland; Prof. Lewis Kuller, MD, DrPH, University of Pittsburgh; Prof. Ruey-Shiung Lin, MD, MHS, National Taiwan University; Dr. Kiyohiko Mabuchi, MD, MHS, Radiation Epidemiology Branch, NIH; Dean Phillip Pizzo, MD, Stanford University; University Prof. Roger W. Sherwin, MB BChir, University of Maryland; and Prof. Frank E. Speizer, MD, Harvard Medical School. Prof. Laure Aurelian Kessler, my wife, dearest friend, and colleague, provided unbounded support to complete this vital task, including her virological, immunological, and epidemiological commentary on the HSV-2 virus and its associated roles in human diseases. Sincere thanks are due Rebecca Gladders, Senior Commissioning Editor, Amanda Millar and Sophie Edminson of Cambridge Scholars Publishing for their valuable assistance.

THE PAST

CHAPTER ONE SUMMARY

MEDICINE EVOLVES FROM FAITH TO SCIENCE

For most of recorded history, people relied on gods and medicine men to diagnose and treat their illnesses. The first medical schools were established 18 centuries after the Hippocratic Oath began urging caregivers and their students to obey basic moral principles in their clinical practice. Until modern times, tribal groups accepted certain vegetables, fruits, and animal products as being healthful on the basis of observations by community leaders and others, using their senses of taste and smell and the physical consequences of ingestion. Foods with laxative, medicinal, or poisonous effects were similarly accepted or rejected for thousands of years.

In the absence of science-based knowledge, the core principles of systematic sanitation practiced by the Israelites defended them against infectious disease long before the appearance of science-based medicine. The faith-based laws of Kashrut, such as washing the hands before meals, certain food practices, bodily cleansing after contact with discharges from themselves or others, and circumcision, were adopted by the world's Muslims around 600 AD and by millions of other non-Jews in today's Western-oriented countries.

After analytical and microscopic studies began to challenge the ancient, but stagnant, views of Galen, Ramazzini undertook the first epidemiological investigations of diseases in workers exposed to a variety of toxic substances. By the mid-1800s,

medical science had advanced remarkably in formulating germ theories of disease, Koch's postulates to prove that microbes are causes of specific illnesses, vaccine development, and technical breakthroughs like stethoscopes and X-rays to study vascular circulation and a host of other human conditions.

This chapter highlights the prodigious discoveries of a number of bioscientists who accelerated the evolution of medicine from faith to true science. Vesalius disproved many of Galen's anatomical theories, Harvey clarified the roles of the heart, lungs, and blood vessels, and Malpighi discovered the basic roles of the skin and blood vessels, while van Leeuwenhoek and Kohler dominated the development of microscopy.

Ramazzini's research, though flawed, called attention to risk factors that exist in many diseases and need to have their causative roles investigated. The work of John Shaw Billings led to the Hollerith card and, from there, to the giant computer industry of today.

While all of these medical and technical developments represent spectacular advances in the science of medicine, the remarkable achievements in epidemiology attracted far less attention. This paradox may be related to the fact that clinicians use microscopes, stethoscopes, and X-rays daily in their clinical practice, but read about epidemiological studies only in their leisure.

CHAPTER ONE

MEDICINE EVOLVES FROM FAITH TO SCIENCE

For most of recorded history, people relied on gods and medicine men to diagnose and treat their diseases. The first medical schools were not established until 18 centuries after promulgation of the Hippocratic Oath on the ethics of caregivers, after which systematic observations began to be made and theories on health and disease were formulated.

Until modern times, many tribal groups around the world came to accept certain vegetables, fruits, and animal products as being healthful on the basis of observations by medicine men, community leaders, and others, using their senses of taste and smell and the physical consequences of ingestion, ranging from gastrointestinal upsets and allergies to severe infections and death. Foods with laxative, medicinal, or toxic effects were similarly identified and accepted or rejected for use in an essentially unscientific fashion for thousands of years, until the gradual emergence of medicine as a systematic approach to organizing random medical observations into a scientific discipline. The ancient cultural practices of India and China, with particular reference to animals approved or rejected as food, have been incorporated into the religious practices of different segments of their populations, with vegetarian diets mandated by Hinduism, Jainism, and Buddhism.

An exceptional prototype of sanitary health recommendations dating from the second millennium BC was reiterated

throughout the Hebrew Bible and Talmud, and maintained for over 3,000 years. These religion-based health and behavioral practices of Kashrut were adhered to over this extraordinary length of time because they proved to be sufficiently effective in warding off disease and maintaining health. The hygienic practices included washing the hands before meals, bodily cleansing in fresh water after contacting discharges from themselves or others, burying human waste, and a variety of food practices.

In the absence of science-based knowledge, the core principles of systematic sanitation practiced by the Israelites defended them against infectious disease eons before the development of Pasteur's explanations of infectious diseases and their prevention. Related health laws required burning the clothes of leprosy victims, quarantining patients with a variety of infectious diseases, and frequent washing of patients and their clothing. Circumcision was another major, and still somewhat controversial, Hebraic health practice, which was adopted by the world's Muslims around 600 AD and millions of other non-Jews in today's Western-oriented countries. The benefits of this procedure—such as a reduced risk of phimosis in men and of cervical cancer in their wives and sexual contacts—have been attested to in many studies. Over its multiple-century history, Kashrut involved adherence to dietary laws by most Jews until modern times. This forbade the intake of swine, a major source of trichinosis, and certain seafood, and encouraged diets based on fruits, vegetables, and kosher meats. The extent to which these dietary laws affect health and disease remains indeterminate, although the continued practice of Kashrut over millennia makes it worthy of continued study.

After the initial appearance of anatomical and microscopical studies challenging the stagnant views of Galen of Pergamon (130–210 AD), Bernardino Ramazzini undertook pioneering epidemiological investigations of diseases in workers of the late 1600s who were exposed to chemicals, dust, metals, and other toxic substances. His research, though technically flawed, was the first to demonstrate how one might compare exposure to disease risk factors among workers in specific occupations with their counterparts in the general population.

By the mid-1800s, medical science had advanced sufficiently to formulate germ theories of disease, Koch's postulates to prove that microbes are the causes of specific illnesses, the development of vaccines, and technical breakthroughs like stethoscopes and X-rays to investigate the vascular circulation and a host of other clinical conditions. The Library of the Surgeon General, established to study the medical outcomes of the Civil War, led to a method of storing vast amounts of medical information on Hollerith cards, an important precursor of the modern computer. And, late in the 19th century, following the brilliant work of Robert Koch, Louis Pasteur, Marie Curie, and other bioscientists, research institutes devoted to biomedical education and research were established at major medical schools in Europe and the United States.

The Hippocratic Oath, an ancient ethical code to promote beneficence and non-maleficence among all practitioners of medicine and their students, was promulgated by a Greek physician, possibly Hippocrates, about 1,500 years before the first medical schools were organized in Italy and France, demonstrating the significance of health and disease to the public long before medical science had begun to evolve.

MEDICAL SCHOOLS BEGIN WITH GROSS ANATOMY

During the Renaissance, knowledge of human and animal anatomy gradually began to be acquired through dissections, often conducted secretly on cadavers secured outside the law, in Italy and other Western European countries. These studies eventually led to the development of the first subject matter of modern medicine, viz. anatomy, beginning with gross anatomy based on cadaver research and direct examination of patients, living and dead. Paramount among the early anatomists was one of the world's great geniuses, Leonardo da Vinci. This remarkable observer of nature and life in the late 15th to early 16th centuries achieved world renown for his extraordinary art and unusual scientific brilliance, both medical and physical. The painter of the *Mona Lisa* and the *Last Supper* was also the most talented anatomist of his time, drawing and commenting on many aspects of human anatomy, dissection, and comparative anatomy.

Medical schools began to be established in the early 13th century, by which time European society was concurring that sufficient knowledge had been amassed to justify the inclusion of medicine in its universities. Physician training was inaugurated in Salerno and Montpellier at the universities of Bologna and Padua, in the early 1200s. The emphasis was on the recently accumulated anatomical details of the human body, derived largely from human dissection, as well as formal critiques of the thousand-year-old observations of Galen of Pergamon, which had barely been modified during this millennium. It is not surprising that the central focus of the newly established medical schools was human anatomy and the structures and functions presumed, though not validated, of the organs of the body. There was little objective

evidence from any other source, except clinical observation of patients over the course of their diseases.

Among his contemporaries, Andreas Vesalius, a Belgian, was universally regarded as the founder of modern human anatomy. He devoted much of his career to disproving many of Galen's anatomical theories, fomenting antagonism from the orthodox "scientific world" that `regarded opposition to Galen as blasphemous. Vesalius discovered, for example, that many of Galen's observations were based on ape, rather than human, anatomy, and that the lower human jaw was a single bone rather than two, as in animals. But Vesalius also perpetuated errors; for example, though he fairly accurately described the anatomy of the brain, he continued to teach that the heart and ventricles were the main sites of brain function. His teaching methods also generated controversy, as they involved anatomical dissections with the active participation of students, rather than simple acceptance and regurgitation of the 1,400-year-old views of Galen.

While several centuries of anatomical observations and debates finally led to a resolution of some major questions regarding human anatomy, other advances in medicine were also occurring during the Renaissance. Among the most significant were the clinical observations on blood circulation proposed by William Harvey, an English physician who studied medicine at Padua and spent most of his life as Physician in Charge at St. Bartholomew's Hospital in London during the 1600s. Married, but childless, he lived a modest life, examining patients and lecturing extensively but also occupying politically important positions in later life to the British monarchy and the College of Physicians. His brief but very influential text, "De Motu Cordis," conflicted with many teachings of Galen but came much closer to clarifying the true

functioning of the heart, lungs, and blood vessels in animals and man.

However, two major facts eluded him: first, he could never demonstrate his hypothesized blood vessels (capillaries) that would have proven the single circuit of blood circulation; and, second, he could never explain why the heart should circulate blood (i.e. the role of oxygen).

One of the first notable microscopists seeking to expand medical knowledge beyond that revealed by gross anatomy was Marcello Malpighi. After earning his medical degree at Bologna in 1653, he devoted the rest of his life to the gross pathology of hundreds of autopsies and their correlation with the signs and symptoms of disease appearing prior to death. His microscopic observations of the human body often contradicted the still dominant views of Galen and his unscientific, but still popular, medical beliefs.

Malpighi made fundamental discoveries concerning many internal organs as well as the skin and red blood cells. He also provided the missing link in William Harvey's theory of a single circuit of blood circulation by describing the pulmonary capillaries that connect the small veins to the small arteries in the bloodstream. But, as is true for many brilliant scholars throughout the history of medicine and science, many of his conclusions concerning cell and organ function were erroneous.

In the late 1600s, Antonie van Leeuwenhoek, a Dutch draper, developed an interest in lens making and microscopes in order to study the microscopic world. Beginning with lice, bees, and mold, his studies eventually led to visualization of bacteria, spermatozoa, and cell vacuoles, inter alia. The development of

microscopes led to major advances in anatomy and promising ideas about blood, the arterial and venous circulatory systems, the heart, the lungs, and other bodily systems. It eventually led to a fuller understanding of microbes, beginning with various bacterial species, as the bearers of disease. While Malpighi was the pioneering gross pathologist of his era, it was Rudolph Virchow 50 years later who focused attention on manifestations of disease at the cellular level and is credited with being the father of microscopic pathology.

The next great development in microscopy did not occur until late in the 19th century when August Kohler developed a new technique for sample illumination (Kohler illumination), which eventually led to phase contrast microscopy, permitting the imaging of colorless and transparent samples, and, later on, to the electron microscope that discerned objects as small as the diameter of an atom in the early 1930s. Other microscopic tools for research and medical care were developed more recently, including transmission and scanning electron microscopes, which produce three-dimensional images of objects down to the atomic level, as well as fluorescence and confocal microscopy.

ADVENT OF EPIDEMIOLOGY

Late in the mid-17th century, by which time some of the basic elements of scientific observation and experimentation had been established, Bernadino Ramazzini, a medical school professor in Modena and Padua, initiated the first systematic study of the health of workers and tradesmen, suggesting the possible disease-causing capabilities of chemicals, dust, metals and other occupational exposures. But his famous book, written before any fundamental knowledge of infectious agents, genetics, chemicals or other agents of disease or

disability had been demonstrated, was a revolutionary but futile effort to identify actual diagnostic or preventive criteria for disease. His text, like many written by brilliant scholars before medical science had sufficiently advanced, was a lengthy narrative offering an unsubstantiated view of the diseases most characteristic of workers in a variety of occupations, including "Jewishness"! Ramazzini's research, though fatally flawed scientifically, was the first to demonstrate how one might compare the quantitative and qualitative aspects of associations between exposure to risk factors (e.g. a specific chemical, metal or dust) in specific occupations as compared to the same associations in the general (largely unexposed) population of similar age.

Ramazzini's approach, though lacking the elements of modern biomedical science, represented an early and pioneering development in classical epidemiological thinking. He systematically searched for risk factors in patients with specific diseases that might play a role in their pathogenesis and compared their prevalence with people in the general population. In modern epidemiology, this process is accelerated: patients with a given disease are identified, their symptoms, complications, and outcomes are observed, and comparisons are made with the general population.

Domenico Rigoni-Stern was an Italian surgeon in Verona who was actively interested in the epidemiological distribution of human disease. He undertook a statistical analysis of cancer incidence and mortality based on data from Verona between 1760 and 1839. Despite a number of arithmetic and medical errors, the data revealed that more women than men died from tumors and that, among women, neoplasms of the breast and uterus were the most common. He also suggested that cancer

incidence increases with age and dwelling in urban areas, and unmarried people are most susceptible to it.

The outbreak of a cholera epidemic in 1854 attracted the attention of an English physician, John Snow, an early supporter of the germ theory of disease. He lived near Soho, London, and suspected that a contaminated water pipe near the intersection of Broad Street and Cambridge Street was the source. He amassed patient data from hospital and public records on whether the victims drank from the pump and concluded that this was the origin of the outbreak. He brought his epidemiological data to the town's officials, the pump was immobilized, and the cholera epidemic ended. His was a remarkable demonstration of clinical epidemiology in action.

Modern medicine arose in the 19th century with great advances in chemistry and bacteriology, but was also accelerated by technical developments including the introduction of the stethoscope for auscultation of lung and heart sounds by Rene Laennec in 1816, and Edward Jenner's discovery of vaccination, i.e. inoculation of cowpox virus to build immunity against the deadly scourge of the related smallpox virus.

The Hungarian physician Ignaz Semmelweis dramatically reduced childbed fever and daringly insulted many physicians of his day in the mid-1800s by suggesting that they wash their hands before undertaking obstetrical procedures, and by recommending antiseptic and aseptic operating rooms. Believing that puerperal fever was caused by "infective material," he required doctors at his hospital to wash their hands in a chlorinated solution before attending patients, and thus reduced the mortality rate for new mothers from 18% to 2%. But it was not until the germ theory of disease was proven, 25 years later, that his theory was finally accepted.

Joseph Lister, a Scottish surgeon, read about Pasteur's research showing how wine spoiled because of microorganisms in the air. This convinced him, in the mid-1800s, that similar organisms also caused the infections that killed up to half of his patients after successful surgery. By cleaning surgical wounds and instruments with carbolic acid mists, he reduced the death rate from 46% to 15%. His widely publicized success revolutionized the use of aseptic and antiseptic measures in surgery. The germ theory of disease began to clarify disease etiology and rationalize methods for controlling infectious disease. It also stimulated the development of public health measures such as quarantine and sanitary treatments of toilet and garbage collection, as had been mandated to the Israelites three millennia earlier. Overall nutrition also began to improve health in the Western world, as did the national economies despite totalitarian governments and dreadful wars.

COMPUTER SCIENCE EXPEDITED BY WARFARE

The US Civil War served as a major training ground for the treatment of wounds and accidents that kill or incapacitate many more soldiers than actual battles, and led to more effective methods for the treatment of infectious diseases. Surgical techniques, nursing care, hospital organization, and even biomedical research all benefited, even in the absence of antibiotics that had not yet been developed. World Wars I and II advanced the treatment of massive injuries and control of infections rampant under battlefield conditions. Greatly improved types of prosthetic limbs, plastic surgery, and cosmetic surgery were introduced, and experience was gained with the first widespread use of antibacterial agents such as the sulfa drugs in World War I. Shortly thereafter, a major advance in the care of the wounded with tetanus immunization was achieved, and treatments with penicillin,

the sulfa drugs, and DDT as an insecticide against malaria vectors were all found to be highly effective.

A senior surgeon in the Civil War, John Shaw Billings, founded the Library of the Surgeon General, now the National Library of Medicine, initially to deal with the enormous amount of statistical data collected by the Sanitary Commission during and after the Civil War. His objective was to store the information and develop methods to access it rapidly while searching mechanically for data patterns. Billings and his associate, Herman Hollerith, discovered how to turn facts into numbers, and punch the numbers onto cardboard cards that could be sorted and counted by machine. The punch card and counter-sorter system that dominated statistical data manipulation until the 1970s became the International Business Machines (IBM) Corporation in 1911.

Care of the insane was largely a family responsibility, rather than a medical or community problem, until the 19th century. In that era, lunacy was seen less as a medical disease than a mental and moral one, and the recommended treatment was largely persuasion and internal restraint rather than coercion. “Moral treatment” centers were built throughout Europe and America and medico-psychological journals emphasizing this viewpoint were published, but, by the end of the century, optimism that asylums could treat insanity declined and the public began to view the insane as suffering from specific causes, including heredity. The German physician Emil Kraepelin introduced new categories of mental illness often based on behavior, such as shell shock in soldiers. In the 1930s, a variety of controversial practices were introduced (electroshock, insulin, lobotomy, etc.), and in the 1950s new psychiatric drugs, such as chlorpromazine, began to be produced in the biomedical laboratories.

A critical discovery at the turn of the century was the ABO blood group system and, in 1937, the Rhesus group, which greatly facilitated blood transfusion and other important procedures. General anesthesia with ether played an essential role in most surgical procedures and in research for nearly a century. It was first used in the early 1840s after trials with nitrous oxide (laughing gas), chloroform, and cocaine were found to be less effective. Dr. William Morton offered the first public demonstration of its utility in the Ether Dome at the Massachusetts General Hospital. By the 1940s, the non-flammable Pentothal and Halothane replaced the use of ether worldwide. The achievement of effective and safe general anesthesia greatly accelerated the rate at which medical science progressed from the pre-modern era into the modern era.

Medical practice changed dramatically throughout the 19th century as a result of advances in biomedical technology, such as the stethoscope, microscopy, and ether anesthesia. Much was learned about microscopic and cellular pathology in the presence or absence of specific disease. But the decline in many lethal diseases at that time was more attributable to improvements in public health, sanitation, and nutrition than to any specific medical techniques. Advances in bacteriology, virology, pharmacology, and related disciplines did not register much of an effect until the first decades of the 20th century.

BACTERIOLOGY AND GERM THEORY

Germ theory, and the development of modern bacteriology, began in the second quarter of 19th-century Italy when Agostino Bassi traced the silkworm disease muscardine to microorganisms. At around the same time, Theodore Schwann,

a German physician, conducted research on alcoholic fermentation by yeast, and proposed that living microorganisms were involved in the process. His claim was derided by Justus von Liebig and other leading chemists who were seeking a physicochemical explanation, rather than one involving a living process. Louis Pasteur of France confirmed Schwann's fermentation experiments, insisting that yeasts are microorganisms, and suggested that this might explain contagious diseases. His observation of bacterial fermentation in butyric acid led to Casimir Davaine's determination that bacteridia, a similar species, was the pathogen of anthrax, a serious disease in the cattle industry, although this was a theory that had been rejected by most bioscientists of the time. In 1898, the German researcher Emil von Behring discovered that immunity to diphtheria could be produced by injecting diphtheria toxin neutralized by diphtheria antitoxin into laboratory animals, a discovery recognized by a Nobel Prize in 1901. By 1913 he had developed toxin and antitoxin mixtures that successfully banished diphtheria and tetanus as scourges of mankind, thereby introducing modern methods of immunization into clinical practice and medical education.

It was only in the late 1800s that Robert Koch, a brilliant German physician skilled in the emerging microbiological advances of that era, and his associate Friedrich Loeffler, proposed testable postulates underlying causal relationships between microbes and disease (Koch, 1884, 1-88; Loeffler, 1883, 421-499). They inoculated laboratory animals with bacterial spores to cause anthrax—a spectacular confirmation of the germ theory of disease and a landmark in experimental pathology. A few years later, they discovered the tubercle bacillus, grew it in pure culture, and thus further validated Koch's germ theory. In later years Koch made a controversial decision, later confirmed, that bacilli causing human and

bovine tuberculosis were not identical. When a severe cholera epidemic broke out in Alexandria, Egypt, Koch and Pasteur both sent research teams to investigate. Koch's team discovered the cholera pathogen and returned to Germany to face serious debates with Max von Pettenkoffer, who opposed water treatment as being misdirected and downplayed a direct pathogenic role for the gram-negative vibrio cholerae bacterium. Nine years later, a massive cholera epidemic in Hamburg devastated Pettenkoffer's position and "Koch's bacteriology" was accepted.

Beginning with tests for cholera and tuberculosis, the principles of germ theory were later applied to numerous other infectious diseases. Koch's postulates are critically important in establishing the criteria for determining that a microorganism causes a specific disease. His original postulates were the following: (1) The infectious agent must be present only in diseased individuals; not in healthy individuals; (2) The agent must be isolated from the diseased person and cultured in vitro; (3) Inoculation of another healthy individual with the cultured microorganism must recapitulate the disease in the subject from whom the agent was originally isolated; (4) The microorganism isolated from the subject who developed the disease after receiving the in vitro cultured agent must be identical to the original microorganism (Koch, 1884, 1-88; Loeffler, 1883, 421-499).

Like much else in science, modifications and adaptations of seemingly fixed "unrevisable" principles often follow initial "incontrovertible" pronouncements. Thus, it was not long before asymptomatic carriers of cholera and typhoid fever were discovered, which thus necessitated a modification in Koch's first postulate. In subsequent decades, asymptomatic or subclinical infection carriers were identified as a common

feature of many viral infectious diseases, such as poliomyelitis, herpes simplex, HIV, and hepatitis C. The second postulate turned out to be inappropriate for detecting microbes that cannot be grown in pure culture, such as Creutzfeldt-Jacob disease. The third postulate is now considered as less than absolute because not all organisms exposed to an infectious agent will acquire the infection due to the host's good health, immune status, acquired immunity from previous exposure, vaccination, or genetic immunity (e.g. resistance to malaria conferred by a sickle cell allele). Koch's postulates also cannot be employed for viruses that do not replicate in cell culture, or for which a suitable animal model cannot be found. Genomic and proteomic data are now contributing to our understanding of Koch's postulates in disorders, which are not directly traceable to infection (Segre, 2013).

KOCH'S POSTULATES AND VACCINES

When Pasteur's team returned to Paris from Alexandria after losing to Koch, they changed the direction of their research to the development of a third vaccine (against rabies, a deadly disease caused by viral infection of the central nervous system). This was only the second vaccine developed for humans since Jenner's (for smallpox), and it attracted much favorable attention to Pasteur and his colleagues fighting infectious diseases. The Pasteur Institute, the world's first biomedical institute, opened in 1888 and played a leading role thereafter in microbiology and medicine. Pasteur was greatly honored for his work, receiving the Grand Croix of the Legion of Honor. In 1895, the year of his death, he was awarded the Leeuwenhoek medal, microbiology's highest honor. He would certainly have won a Nobel Prize had he lived. His German counterpart, Koch, was honored with a Nobel Prize in

1905. Another observation on the awards: in 1897, a dissertation by Ernest Duchesne, a Pasteur researcher, on the use of Penicillium glaucum to cure infections was ignored by the scientific community for reasons still unknown to this day. One wonders about the millions of lives that could have been saved, had his discovery been exploited!

The Pasteur Institute, now with over 500 researchers, recently celebrated its 125th anniversary. It was established six years before the Nobel Committee made its first awards. Modern nucleic acid-based microbial detection methods have reduced the relevance of Koch's original postulates, as it is now possible to identify microbes associated with a disease that are uncultivable. Present-day methods have also become so sensitive that they can often detect extremely low levels of viruses that are commonly found in healthy people without disease.

Because of the importance of correctly detecting the presence or absence of disease in the clinical setting, as well as during the course of biomedical research, revised versions of Koch's postulates have been proposed in more recent times. For example, Fredericks and Relman (1996, 18-33) suggested the following postulates:

1. A nucleic acid sequence belonging to a putative pathogen should be present in most cases of an infectious disease. The sequence should be found preferentially in those organs or gross anatomic sites known to be diseased and not in organs lacking pathologic evidence of disease.
2. Fewer, or no, copies of pathogen-associated nucleic acid sequences should occur in hosts or tissues without the disease.

3. As the disease resolves in the host, the copy number of pathogen-associated nucleic acid sequences should decrease or become undetectable. And, with clinical relapse of the disease, the opposite sequence should occur.
4. The association between pathogen-associated nucleic acid sequences and the disease is more likely to be causal when the detection of the sequence predates the disease, or when the sequence copy number correlates with the severity of the disease and its pathology.
5. The nature of the microorganism inferred from the available nucleic acid sequence should be consistent with the known biological characteristics of that group of organisms.
6. Correlations between pathogen-associated nucleic acid sequences and host tissues should also be sought at the cellular level. Efforts should be made to demonstrate specific in situ hybridization of microbial sequences to areas of tissue pathology and to visible microorganisms or to areas where microorganisms are presumed to be located.

Even after modern science develops objective criteria for deciding whether a microbe is the cause of a disease, there is not always agreement among scientists for a variety of reasons, including political considerations. An example of how a microbe fulfilling most biomedical, clinical, and epidemiological criteria for being the cause of a disease can be rejected in favor of another microbe, which also fails to fully satisfy the criteria, is offered by cervical cancer. After several decades of numerous and well-designed animal and human studies, including controlled clinical trials, demonstrated that the herpes simplex virus type 2 was a likely cause of human cervical cancer, the 2008 Nobel Prize in Medicine was

awarded to a German scientist for discovering that the human papilloma virus (HPV) was the cause of this disease. It should be noted that HPV is epidemiologically and clinically inconsistent with causing cervical cancer, and the biomedical reasoning leading to its presumed causal relationship remains unconvincing. Biostatistical studies have demonstrated that the incidence of cervical cancer has not declined years after the massive use of an HPV vaccine in women (Chapter 7).

X-RAYS AND RADIOACTIVITY

Toward the end of the 19th century, two highly significant discoveries were made that applied to the science of physics but also were important in the advance of medical science. The first of these, the X-ray, was made by Wilhelm Roentgen, a pampered child of wealthy Prussian parents who was expelled from school and failed the college entrance examinations, but eventually graduated from an engineering school and began teaching physics, without a salary. Eventually becoming a professor at Wurzburg, he discovered the X-ray in 1895 and was awarded the Nobel Prize in Physics in 1901. This marked a great advance in the world of physics, of course, but was also a boon to biomedical research in providing an essential tool for the detection of certain diseases.

The second great breakthrough following Roentgen's discovery of X-rays concerned the spontaneous radioactivity of uranium. Henri Becquerel, a fourth-generation physicist-engineer from a distinguished Parisian family, was interested in the plane polarization of light, phosphorescence, and the absorption of light by crystals. He decided to investigate whether there were any natural links between X-rays and phosphorescence. When he placed uranium salts near a

photographic plate covered with opaque paper, the plate became fogged. This phenomenon turned out to be shared by many uranium salts and led to the conclusion that it was a property of the uranium atom. Becquerel later showed that the rays emitted by uranium caused gases to ionize and differed from X-rays because they could be deflected by electric or magnetic fields. For his discovery of spontaneous radioactivity, Becquerel shared the Nobel Prize in 1903 with Pierre and Marie Curie.

Marie Curie, née Maria Sklodowska, was born into an educated Warsaw family impoverished by the political division of Poland among the Russian, Prussian, and Austrian empires. She lost a sister to typhus and her mother to tuberculosis by age 10, but, because of her sex, was barred by the Russian government from attending university. She enrolled in a few privately sponsored academic courses, while devoting time as a governess earning a few zlotys each week in a neighboring town.

In 1891 Curie finally succeeded in moving to Paris and enrolling as a physics student at the Sorbonne. From this point onward her professional life became sensationally successful, although income remained problematic and her personal life continued to have its share of personal tragedies. The year before graduating in physics and mathematics, she met Pierre Curie—a physicist at the University of Paris—married him, and undertook an extraordinary collaboration in scientific research with him.

In the year of the Curies' marriage, 1895, Roentgen had discovered X- rays, though little was known about how they were produced. The following year, Becquerel ascertained that uranium salts emitted rays that resembled X-rays in their

penetrating power, but that this radiation, unlike phosphorescence, did not depend on an external source of energy but seemed to arise from the uranium itself. These discoveries led Marie into examining uranium rays as a possible thesis research topic. Using an electrometer developed by Pierre and his brother 15 years earlier, she discovered that uranium rays caused the air around each of her samples to conduct electricity, and that the activity of the uranium compounds depended only on the quantity of uranium present. She hypothesized that the radiation was not the outcome of some interaction of molecules but that came from the atom itself. The hypothesis also suggested that atoms were not necessarily indivisible.

Marie then exposed two uranium minerals, pitchblende and chalcocite, to her electrometer, and found that pitchblende was four times as active as uranium and chalcocite was twice as active. This led her to conclude that these two minerals contain another substance far more active than uranium. Shortly thereafter she discovered that the element thorium was also radioactive. Pierre became enthusiastic about Marie's research, and from1898 on, discontinued his own crystal research and joined her radioactivity studies. Later that year the Curies published a joint paper announcing the existence of an element named "polonium" in honor of her native land, and by the end of the year they announced the existence of "radium," each isolated from pitchblende. At the same time, they coined the term "radioactivity."

To prove their discoveries beyond any doubt, the Curies then sought to isolate polonium and radium in pure form, which was an extremely arduous task. From a ton of pitchblende, they separated out one-tenth of a gram of radium chloride after enormous effort. Eight years later Marie isolated pure

radium metal. She was never able to isolate polonium because its half-life of 138 days was too short. Marie was very cognizant of the beneficial uses of radium in medicine, and she demonstrated in a paper that, when exposed to radium, tumor-forming cells were destroyed faster than healthy cells. But no effort was made by her to patent this discovery, which rapidly became a very profitable business worldwide.

Pierre and Marie Curie shared the 1903 Nobel Prize in Physics, together with Henri Becquerel. Marie was the first woman to be so honored, but only after overcoming much anti-feminist opposition. With the award, the Curies were able to hire their first laboratory assistant. But, only three years later, Pierre was tragically killed in a traffic accident, leaving Marie once again bereft of research funding. She was awarded a second Nobel Prize in Chemistry a few years later for her discovery of radium and polonium and, at about this time, accepted the offer of a chair in physics at the University of Paris. She was thus the first female Nobel Prize awardee as well as the first female professor at the university. A few years later, the Pasteur Institute and the University of Paris created the Radium Institute, now the Curie Institute, which she also headed. During World War I she developed mobile radiography units for the French Army to assist battlefield surgeons in treating the wounded. Throughout all of her professional life, she was attacked by anti-feminists, by anti-Semites who falsely accused her of being Jewish, and by a variety of professional colleagues who were primarily jealous of this brilliant woman. She died in 1934 of aplastic anemia, contracted from lifetime exposure to radiation. As a final belated honor to her memory, her and Pierre's remains were interred 60 years later in the Pantheon, she being the first woman so honored.

ESTABLISHMENT OF BIOMEDICAL RESEARCH INSTITUTES

Until late in the 18th century, advances in biomedical research were largely the result of physicians and other scientists working independently. Eye glasses, microscopes, stethoscopes, citrus fruits preventing scurvy, smallpox vaccination, antiseptic surgery, and prevention of puerperal fever were all advances of this type. But, beginning in the last quarter of the 19th century, biomedical research institutes associated with medical schools began to appear, primarily in France, Germany, and Great Britain. These institutions housed multiple researchers with a variety of educational and research interests, which could be utilized whenever national or worldwide health issues arose. The acquisition of new faculty and interested students was facilitated by the associated medical school, and research funding became an institutional responsibility. Over the years, most of the research institutes came to be dominated by their affiliated medical school, while a few retained their independence.

In France, two biomedical research institutes centered on the research interests of their founders, Marie Curie and Louis Pasteur, were established and both, after their founders' deaths, expanded their research into worldwide infectious and even non-infectious arenas. Each developed formal and informal associations with major universities in order to recruit outstanding faculty and to identify students with high potential to join their ranks. For many years they also attracted funds from pharmaceutical and other biomedical firms, as well as the government and the general public, to support local and worldwide research and training programs. For the Pasteur Institute, opening a research branch in Saigon to prepare vaccines and treat rabies and smallpox was the first

of a host of facilities opened in many parts of southern Asia, Africa, and the Mediterranean. The Curie Institute, the Maria Sklodowska Institute of Oncology in Warsaw, and the Marie Curie Cancer Care movement in Great Britain continue her interests to this day. In their widespread activities, the Curie and Pasteur Institutes resemble many of today's public and private interdisciplinary biomedical research centers.

The discovery of insulin and its modifications in the treatment of diabetes mellitus, one of the most significant biomedical breakthroughs in modern medicine, involved the independent research of a sizable number of researchers in Germany, Great Britain, Canada, and the United States. In 1869, Paul Langerhans, then a medical student in Berlin, was microscopically examining the structure of the pancreas when he noticed some previously unidentified tissue clumps scattered throughout. The clumps, later known as the islets of Langerhans, had no known function until 1889 when Oscar Minkowski, collaborating with Joseph von Mering, removed the pancreas from a healthy dog and noticed swarms of flies feeding on the dog's urine a few days later. Sugar was found in the urine, thus linking the pancreas to diabetes. A few years later, Eugene Opie showed specifically that the disease occurred only when the islets of Langerhans in the pancreas were destroyed. Over the next two decades, several attempts were made to isolate the causative factor in the islets until 1916 when Nicolae Paulescu developed an aqueous pancreatic extract that normalized blood sugar levels in diabetic dogs.

In 1920 Frederick Banting hypothesized that it was the digestive secretions studied by Minkowski that were breaking down the islet secretions, and that the pancreas's internal secretion, by regulating sugar in the bloodstream, held the key to the treatment of diabetes. He convinced JJR Macleod,

Professor of Physiology at the University of Toronto, to grant him laboratory space, ten dogs, and two medical students to test the idea. Since he only needed one assistant, the two students flipped a coin and the winner, Charles Best, won the job and ultimately shared the Nobel Prize with Banting. In their experiment, the pancreatic duct was ligated, killing the pancreatic digestive cells, but sparing thousands of islets. An extract was then isolated from the islets, producing what is now called insulin. The latter was able to maintain the life of one of the pancreatized dogs. Efforts were then made to produce larger quantities of highly refined insulin for clinical use, but the effort failed until Eli Lilly & Company got involved.

Insulin is a peptide hormone, produced by the beta cells of the pancreas, which is central to regulating carbohydrate and fat metabolism in the body. When the control of insulin level fails, diabetes mellitus can result. Patients with Type 1 diabetes depend on external insulin, while Type 2 diabetics are often insulin resistant and may suffer from a relative insulin deficiency. Some patients with Type 2 diabetes may eventually require insulin if other medications fail to control their blood glucose levels adequately.

In 1955 insulin became the first protein to be fully sequenced, resulting in a Nobel Prize for Frederick Sanger who showed that all human proteins have a unique sequence of any, or all, 20 types of amino acids strung together in chains called peptides. Human insulin has two peptides: the A (acidic) chain with 21 amino acids and the B (basic) chain with 30 amino acids. Two sulfide bridges between the sulfur atoms in the amino acid cysteine connect the two chains. A third internal disulfide bridge is also found in the A chain to help hold the molecule together. Insulin is produced and stored in

the body as a hexamer (six insulin molecules), while the active form is the monomer.

If a protein's sequence is known, it is possible in theory to recreate it synthetically, and insulin was the first protein to be chemically synthesized in a laboratory in 1963. The amino acid structure of insulin was characterized in the early 1950s and the first synthetic insulin was produced a decade later. But because so little could be produced, diabetics had to rely on hormone produced from animals (cattle and pigs) after Banting's group isolated insulin. Animal-based insulin is not an exact match of the human hormone, which thus permits skin rashes and other adverse reactions to occur. For sixty years, purified insulin from animal sources was the only type of insulin available to diabetics until genetic advances began to play an important role in biomedical research. Finally, in 1978, the first genetically engineered synthetic "human" protein was manufactured through biotechnological means using E. Coli by collaborating research teams at the City of Hope Hospital and Genentech, a newly formed biotechnology company. The gene for human insulin was inserted into bacterial DNA, using the bacteria as miniature factories to make the A and B chains of the protein separately. In a separate step, a chemical process combined them, producing humulin, or recombinant human insulin, without the problems of animal insulin. Shortly thereafter, Genentech and Eli Lilly & Company began to sell the first commercially available biosynthetic human insulin under the brand name Humulin.

Most insulin in use today is biosynthetic recombinant "human" insulin or its analogues produced either in yeast or E. coli. It is interesting to note that the porcine and cattle insulins used for so many years were effective because they differed so little from the human type: by one amino acid in

pigs and three in cattle. That insulin has been in the forefront of the new biotechnical era of science for so many years is exemplified by the fact that no less than four Nobel Prizes have been awarded over half a century for insulin-based research, including Banting and MacLeod in 1923, Sanger in 1958, Hodgkin for determining the spatial conformation of the molecule, and Yalow for developing the radioimmunoassay for the enzyme. It is also notable that George Minot, co-discoverer of the first effective treatment for pernicious anemia and a diabetic, was kept alive by insulin while engaged in his own research.

The study of insulin and diabetes has been a major focus of attention in biomedical science for nearly 150 years and its methods are highly representative of those in use since the third decade of the 19th century. Beginning with the rather primitive methods of pancreatectomy and isolation of its secretions to the production of human insulin through injection of the human gene into safflower plants, the steady progress of biomedical research is clearly evident. Production costs of insulin have been reduced, and slightly modified versions of human insulin analogues with different absorption or duration of action characteristics are now available to meet a variety of patients' needs. Unfortunately, insulin cannot be taken orally because, like nearly all ingested proteins, it is reduced to small fragments in the gastrointestinal tract with a loss of all activity. At present, companies are already at work trying to produce an oral-insulin alternative.

RECENT MEDICAL ADVANCES

This chapter was written as an introduction to the history of medicine for lay readers interested the role of epidemiology. It does not presume to be an all-inclusive textbook on the subject. The following are some of the discoveries in medicine that were not mentioned in the text:

- Drugs, including penicillin, acetaminophen, tetracycline, oral contraceptives, beta-blockers, and cyclosporine.
- Magnetic resonance imaging, computed tomography, positron emission tomography.
- Cardiac pacemakers, heart-lung machines, electrocardiography, electroencephalo-graphy.
- Chemotherapy, stents, balloon catheters, in-vitro fertilization.
- Transplants of the kidney, liver, lung, pancreas, and heart.
- Cochlear implant, laser eye surgery.

Chapter Two Summary

Epidemiology Flourishes by Applying Scientific Reasoning to Clinical Observations

Medicine evolved from random observations on diseases developing in people, their acquaintances, or others in their neighborhood. Before the advent of the stethoscope, optical lenses, surgical examinations, or other tools for examining patients, it was the perceptive eye of a mother, a neighbor, or even accidental encounters that detected possible illnesses or other discrepancies from the normal status. If such occurrences took place often enough, or in individuals of noteworthy status, they would lead to discussion, retention in the community's memory, and eventual emergence as facts in the health and disease belief system of the population.

As clinical observations accumulated, community leaders and physicians began to systematically sort, classify, analyze, and disseminate disease-related information. Their initially simplistic observations grew in stature with the advent of science, epidemiological reasoning, and biostatistical methods. Bernadino Ramazzini, a medical school professor in 17th-century Modena and Padua, undertook the first systematic studies of disease occurring among workers exposed to environmental factors. While his approach lacked critical features of modern biomedical science, his efforts marked a significant development in the evolution of epidemiology and

biomedical research. Such efforts led to an understanding that disease involves a susceptible host or subject at risk, a causative agent, and an environment favorable to the disease. Among bioscientists, it is the epidemiologist who concentrates his efforts on identifying agents, host factors, and environments that are responsible for diseases in humans to become manifest.

The validity of a study's outcome cannot be inferred directly from the results of any statistical test, but rather from the body of biological data of the patients being studied. In epidemiological investigations, one seeks coherence of a study's findings with existing knowledge about the disease, dose–response effects, confirmation from animal and tissue culture studies, and other replicable results in studies carried out in the bioresearch laboratory or clinical facility.

CHAPTER TWO

EPIDEMIOLOGY FLOURISHES BY APPLYING SCIENTIFIC REASONING TO CLINICAL OBSERVATIONS

EPIDEMIOLOGY AND BASIC SCIENCE

Epidemiology differs from the much larger, and more technically complex, branch of medicine identified as basic medical science. Originally, it dealt with diseases affecting humans rather than animals, although veterinary studies can also be conducted epidemiologically. This approach differs from the research of most basic scientists who employ animals or animal products as their focus of attention, which they accept as being representative of humans in the disease or factor under investigation. While biomedical research uses the methods, tools, and techniques of biology, chemistry, physics, and other basic sciences, epidemiology is a derivative field in which exposures of people with a variety of distinguishable characteristics to presumed risk factors of a disease, and the associated outcomes, are of primary interest.

Those engaged in epidemiology seek to identify the human and environmental factors that play causative or preventive roles in the pathogenesis of a disease. For example, they investigate people of a particular sex, age, constitution, or habits who are exposed to a toxic agent and measure the disease risk experienced. In contrast, the typical biomedical

scientist focuses on basic biomedical factors that underlie, promote, or interfere with the pathogenesis of a disease; for example, a specific array of human- or animal-based genes, viruses, or viral nucleic acids that may affect the health or illness of the host subjects.

While the basic scientist probes for knowledge concerning a potential causal agent of a disease, the epidemiologist searches for relevant information about significant disease-promoting or inhibitory factors by examining the age, sex, race, ethnic group, genomic character, constitutional traits, lifetime occupational exposures, ingested foods and drugs, and a multitude of other experiences that may be linked genetically with the disease uniquely or in combination with other factors. Since all these factors are related, at least in part, to each individual's genomic makeup, the bioscientist and the epidemiologist are both studying disease, though from different directions.

Bioscientists today often investigate the potential role of gene arrays, out of the millions already identified, which have a statistical association of a given power with the disease in question, while epidemiologists apply clinical acumen and probing reviews of the medical literature to identify patient characteristics, including constitutional, behavioral, and occupational exposures, that might (out of millions of potential ones) be causally associated with the disease. With the passage of time, the number of genetic arrays and individual genes causally linked to specific diseases will inevitably increase and the total complement of genes responsible for each disease will be fully identified, thereby reducing the need for epidemiology-based studies grounded on clinical intuition and risk factor associations. Achieving a level of biomedical knowledge sufficient to reveal the cause

or find the cure of a disease will occur at variable times. It is, therefore, likely that the utility of epidemiologists applying their unique reasoning skills in medicine will continue to be essential for decades, or centuries, to come.

RATIONALE OF ANIMAL-BASED STUDIES

During most of the 20th century, the two avenues of biomedical research described above were pursued in most universities and medical schools. The animal-based investigations were aimed at resolving basic scientific issues through experimentation on laboratory animals that were accepted as surrogates for human beings. The popularity of this approach, due to its relative simplicity and low cost compared to studies of human patients, probably accounts for the fact that nearly all Nobel Prizes in Medicine since its inception have been awarded to investigators employing animal-based techniques. Another determinative factor has been the federal government's restrictions and controls over human research, which have multiplied in recent decades, ostensibly to protect the health and human rights of participating subjects. These well-intentioned federal policies, and the state regulations that followed, have played a major role in complicating and, therefore, deterring human studies, the principal research approach of the classical epidemiologist. A third element, largely ignored by the public media, has been the gradual disappearance of clinically trained epidemiologists from medical and public health schools and their replacement by PhD's and other non-physicians primarily interested in the social and economic aspects of disease, rather than its medical etiology.

The rationale for animal-based studies, beyond those with veterinary objectives, is that many, or perhaps most, biological,

pharmacological, immunological, and genetic processes in animals are homologous, or sometimes identical, to those in human beings. This supports the broad conclusion that research on laboratory animals and the analogous relationships of their diseases to the human ones will continue long into the future.

Biomedical researchers who utilize animals as homologues for human subjects usually select commercially available rats, mice, or other homogeneous strains of animals for their studies. The choice of an animal strain greatly simplifies the project, compared with the more complex dilemma of epidemiologists undertaking studies in heterogeneous human subjects. But this advantage is reversed at the next step of the research: investigating human diseases in human subjects is obviously completely objective and pertinent, compared to studies in even the closest animal homologues.

Other advantages of animal-based studies—avoiding the risks of death, infection, injury, pain, bleeding, and other negative outcomes in human subjects, as well as the financial savings—are readily apparent. But the obvious value of studying diseases of man in human patients—despite the higher costs, complexity, and risks to patients—is theoretically, and often practically, incontrovertible. Medical schools and biomedical research institutions should use their influence to convince government agencies to remove politically unnecessary barriers to human studies and to promote the biological reasoning long practiced by both classical basic scientists and epidemiologists.

Over the decades of my professional life I have observed that basic medical scientists prefer, and feel most comfortable with, studying animal proxies rather than human subjects.

Their university training rarely involves human studies, and their understanding of person-based research is often superficial. As long as the practical advantages of homologous animal research are acknowledged, there is little incentive for the medical schools to reopen a candid reappraisal of animal versus human studies, despite the important scientific information being lost and the predictable failures in some animal investigations.

The basic advantages of animal-based studies are as obvious as the well-known shortcomings of human studies. These may be summarized as follows:

1. **Researchers can select for study a species or subspecies of any animal of choice**, expose them to a suspected toxic agent for a lifetime, sacrifice them, and assess the clinical outcomes among all members of the group. Investigations of this kind are not possible in human studies.
2. **Government agencies, and the medical and public health schools, are much less intensively involved in approving animal species for study**, or in terminating or otherwise interfering with this type of research, than they are with human studies.
3. **Study subjects do not volunteer, and non-response need not occur in laboratory animal investigations**. Therefore, the investigator can design protocols that apply to the universe of a species and follow the subjects to the conclusion of an experiment, without concern for dropouts, missing data points, or other problems common in studies of human subjects.
4. **Investigating a truly representative sample of animals is much more readily achieved than any human study,** since all the animals can be examined for

prior and prevalent illnesses, previous exposures, and inclusion or exclusion of genetic or constitutional characteristics than would be case with studies of human subjects.

5. **Achieving a statistically requisite sample size is much more easily accomplished with animal proxies** than with human subjects, who often seek exceptional or special considerations, including payment for their ongoing participation.
6. **Studies conducted on inbred animal strains under highly controlled conditions are much more specific than human studies**. However, even the best-designed animal studies may yield findings that apply only to that specific animal species and are marginally relevant or irrelevant for human beings, because of significant differences in genomes, unidentified environmental factors, and other unknown distinctions in the physiological, pharmacological, hormonal, and other systems of the host animals and their human analogues.
7. **The cost of most human studies, as well as their complexity, is usually severalfold higher than that of most animal studies**, and payments of sometimes lofty fees to participants has become a growing deterrent.
8. **Determining the underlying facts about most issues in biomedicine often requires repeated studies** with or without modification of protocols. This greatly increases the cost advantage of animal studies, but doesn't eliminate the need for human studies.
9. **The animal researcher can obtain whatever endpoint information is required at the end of a study** by any means, including surgery and postmortem observations, which is impossible in human population studies.
10. **Publication of findings in animal studies is usually easier than in human studies**, where restrictions or

exclusions may be requested by the clinicians, next of kin, or even by governmental bodies.

The predominant types of causal studies undertaken prior to the genome revolution were those on animal homologues. Like all experiments, these have a number of inherent weaknesses, which should not be ignored:

1. **Species specificity**: The animal species chosen may differ significantly from humans in metabolic, immunologic, genetic, environmental, behavioral, or other factors governing the risk of developing a disease of interest.
2. **Strains within a given animal species may differ** in their susceptibility to developing the disease of interest, after exposure to the risk factor.
3. **Experimental conditions** may affect the disease outcome, such as the dose of factor; duration of factor exposure; age, sex, or health status of the selected animals; route of administration of the factor to the animals; and presence or absence of co-carcinogens or promoters of the disease under study. Such conditions can also lead to the false assumption that when a presumed factor fails to produce the disease of interest, it may be considered safe for human exposure.
4. **Other complications in drawing biologically relevant conclusions** from animal-based epidemiological studies can occur: when the slope of the dose–response is gradual rather than clear-cut; when there is no apparent threshold dose of the factor required to produce the biological effect; and when the maximum-tolerated dose of the test factor approaches potentially hazardous, or even lethal, levels in the test animals or human subjects.

ADVANTAGES OF HUMAN STUDIES

In view of all these advantages of animal-based studies, what are the benefits of human epidemiologic investigations?

Significant epidemiologic findings often arise from medical observations made during the clinical care of patients with a particular disease, condition, or clinical abnormality. Since the advent of preventive medicine departments and public health schools, cogent discoveries have usually been based on well-designed human studies, often involving exposures of patients to a risk factor (e.g. smoking, a genome, a virus, tobacco, saccharin, etc.) and followed over time or in retrospect for the development of a suspected risk factor or disease. Such investigations usually adhere to the time-honored format of hypothesis formulation, selecting a study group representative of the population at risk, blinding of study personnel to the hypothesis being tested, reducing patient non-response to a minimum, and applying appropriate epidemiological and statistical analyses, after a careful review of the study outcomes.

Diseases befalling humans usually arise from a complex of interactions between environmental conditions and host factors such as genotype, constitution, hormone and immune status, and occupation, inter alia. In view of this, one may argue that **epidemiologic studies conducted in their natural milieu are more appropriate, realistic, and applicable to Homo sapiens than their counterparts in laboratory animal models**, despite the greater costs and complexities. It is the clinical epidemiologist who is the likeliest to carry out human studies in the search for pathogenetic factors of a disease. To assure the continuation of such work, a substantial increase in the recruitment of clinically trained individuals

must occur in our medical and public health schools. The human studies they undertake are necessary today and in the future. They will never be totally replaced by animal research.

With respect to the higher costs of human studies, our recommendations for reviving public health include a number of innovations that will provide substantial additional funding to the proposed Clinical Public Health Departments and their Health Statistics Centers. The new ventures include a series of annual short courses to be offered, in a fee-based fashion, to non-medical professionals whose careers depend on their knowledge of major health and disease issues. One course would be for journalists and journalism students who wish to report on health matters, a second for lawyers and law students to prepare them for roles as defense and prosecuting attorneys, and a third for business executives in the healthcare industry. A second significant venture would have the Health Statistics Center agree to prepare health mortality, incidence, and toxic reports for local, state, and the federal government, a process traditionally given to commercial enterprises. A third important venture would, in calamitous situations such as COVID, recruit the Health Statistics Center to compile and provide politics-free analytical data on the course of serious epidemics (see Chapter 19).

Biomedical research on human subjects, with an emphasis on epidemiological reasoning, was developed in the departments of preventive medicine and public health schools during the early decades of the 20th century. The impetus for this type of research followed discoveries on the microbiological causes of some human diseases—bacterial, rickettsial, and viral—that dominated scientific and public attention worldwide in the initial decades of the 20th century. These discoveries

encouraged the Rockefeller Foundation to endow the establishment of the first schools of public health at the Johns Hopkins and Harvard universities in 1916.

Much of the biomedical research during this period was related to disease-causing organisms and the development of preventive or curative vaccines. A belief among many investigators held that diseases developed in a more complex fashion than by simple-minded interactions between causal agents and the human host. This view encouraged a consensus that scientists should consider the "environment" within which a disease can be successfully induced or prevented in a human or animal host. The environmental factors could involve the host (affecting his immune status), the agent (increased or decreased infectivity), or other conditions that render the host's overall immunity or susceptibility to infection greater or less than expected.

While classic animal-based research continues to dominate within medical schools, the newly established public health schools and their colleagues in preventive medicine departments began to attract physicians and other bioscientists interested in environmental, constitutional, and behavioral factors that might cause, complicate, or prevent diseases initiated by appropriate agents. As time elapsed, and investigations on the influence of host and environmental factors in human disease increased, the preventive medicine departments and public health schools became important centers for investigating such factors, including those linked to specific infectious agents and those not (the chronic diseases).

Like the biomedical studies in medical schools, those conducted in preventive medicine departments and public

health schools were based on sound medical reasoning and specific hypotheses, differing from animal studies only in the procedures employed and in the use of human subjects. In a few of the larger public health schools, animal-based research was also conducted, as well as fundamental research resembling what was already underway in the medical schools. In the early years, most of the public health and preventive medicine researchers were MD or PhD graduates of medical schools, with smaller numbers coming from dental or veterinary schools. Almost all had benefited from a systematic education in the classical medical school courses of that era, including anatomy, microbiology, biochemistry, pathology, pharmacology, physiology, genetics, neuroscience, and immunology, as well as the then developing fields of virology and molecular and cell biology.

IMPACT OF GENOME RESEARCH

Over the next few decades, an influx of faculty educated in a variety of non-traditional medical fields began to join the public health school and preventive medicine faculties, with interests auxiliary to medicine, such as gerontology, sociology, diversity, health economics, etc. This trend paralleled a steady decline in the number of medically trained faculty members, especially after the enactment of numerous federal and state regulations limiting the scope of human epidemiological studies, and an explosion of interest in genomic studies based on the biostatistical analysis of genetic arrays. Eventually, the number of non-medically educated faculty members began to dominate the traditional public health programs, leading to dramatic changes in the research and educational offerings of the public health schools and preventive medicine departments.

Since the advent of the genome era, advances in computer technology and the enormous public interest in social research have dramatically affected how the typical biomedical researcher in a public health school or preventive medicine department approaches his or her work. Instead of initiating a project by carefully reviewing the scientific literature and considering whether a specific hypothesis might explain a biomedical outcome, the effort is now spent in scanning the latest genome information and testing a gene array's biostatistical probability of being associated with a disease or condition of concern. Some in the scientific community now spend much of their time generating odds ratio estimates for the likelihood that their genome, selected from a list of genome arrays compiled by commercial sources, is a causative factor. At the same time, they tend to ignore the accumulated evidence, pro and con, for the involvement of epidemiological factors of disease in the agent, host, and environment.

It is essential that the bioscientific community, and those who fund its research, come to understand that significant gaps in our understanding of disease pathogenesis will remain until hypothesis-based studies are undertaken by more clinically trained epidemiologists. This will occur only if and when the preventive medicine departments and public health schools enhance their abilities to conduct classical epidemiological research on human disease.

The genetic approach dominating research today greatly undervalues the scientific principle of hypothesis formulation in its approach. Articles now appear in major scientific journals that cast doubt on the need to formulate hypotheses before engaging in bioscience—a reflection of a current view that causality can now be explained by a single set of factors

in the genome. A similar type of error occurred during an earlier period when research papers were published on the assumption that a suspect carcinogen could cause a variety of pathologically distinct cancers when administered to laboratory animals. The analyses were judged to be statistically significant if the total number of cancers of any or all types exceeded expectation. Such thinking, implying the existence of nonspecific or multisite carcinogens, delayed progress until scientists, usually PhD's without training in clinical medicine, were re-educated in tumor pathology and related medical disciplines.

While there is overwhelming evidence that genes and gene abnormalities are associated with specific diseases in animals and human patients, biomedical science has concentrated its efforts on the genome. But numerous issues must be resolved before definitive conclusions are made concerning the number and functions of causal genes. Very few diseases have yet been shown to be totally explained by a single gene or gene array. Effective treatments for most cancers and other diseases will have to await the resolution of many unanswered questions, including the following:

1. **Even if patients with a specific disease possess a specific gene, does this indicate that the genome is a necessary and sufficient cause of the disease?** Are other genes, environmental conditions, or host factors (perhaps also genetically related) required as well? Epidemiological studies on human subjects would greatly advance our knowledge on such issues, though such research has been shrinking rather than intensifying at this time.
2. **How many unidentified genetic factors play stimulatory or inhibitory roles in disease pathogenesis**

that have yet to be studied? Such issues also await the results of properly designed epidemiological and genomic studies.

3. **Are there unidentified microbial agents, and environmental or host factors (age, race, sex, diet, smoking, hormonal, dietary, constitutional, occupational, or pharmacologic factors, etc.) that must be involved for a disease to become manifest, in addition to the genetic configuration?** Again, classical epidemiological studies are essential to explore this question.
4. **Are there genetic or agent/host/environment factors that act to prevent the initiation or progression of a disease initiated by other genetic, host, or environment factors?** This largely neglected arena of biomedical research lies substantially in the epidemiologic realm.

Utilizing the computer-assisted genome approach to the study of disease etiology has advanced knowledge, but it has also negatively affected present-day biomedical research and education. It has unduly concentrated research efforts, funding, and expenditure of time on a poorly understood catalogue of risk factors (genes) whose relationships with human disease are only partially known or understood. In the past, biomedical researchers would consider the available evidence for a particular disease in its **demographic aspects** (the sorting of patients, by age, sex, race, locality, etc. at risk), **behavioral aspects** (known or suspected habits, environmental exposures of possible significance, etc.), and **clinical aspects** (prior disease history of patient and family; current physical, physiological, and clinical findings, etc.). Epidemiological reasoning would then be utilized to decide which of these aspects might be causally significant, and potential hypotheses

would then be formulated for study and testing. This process, which usually took months or longer, would eventually lead to testable hypotheses and, often, funded research projects.

The steps described above occur far less frequently these days. Interest has become so overwhelmingly directed at the genome, in which the primary interest is a genetic factor or factors that may be associated with the disease, allowing little consideration of other risk factors active in the host or environment. The investigator peruses listings of genotype combinations largely produced by commercial companies, which also sell array-testing machinery for calculating the relative odds of a particular genotype being present in significantly higher or lower proportions in the test tissue of the study. In these genotype array trials, the statistical test is usually beyond much control or adjustment by the investigator. This discourages the researcher from devoting serious attention to factors other than the selected genomes. And, as noted above, the genome incidence estimate is measured in strictly numerical and statistical terms, rather than in biological terms that include the extent to which the data are epidemiologically consistent. Perhaps thousands of doctoral students are now engaged in the narrowly defined type of genome research described here.

COMPUTING AND BIORESEARCH

As noted above, the influence of easy-to-use computing technology and the development of technical methods to rapidly identify genome arrays have advanced biomedical research, but have also exerted negative effects on research practice and medical education. It is reasonable to assume that medical and public health students presently devote substantially less time to reading medical textbooks and

evaluating the medical literature than was true in the past. In most medical and public health schools, the curriculum has also been continually modified in the direction of shortening classroom and laboratory education in the basic medical sciences. Computer-based self-learning by the students is now regarded as compensating for the elimination of the classroom, but there is little objective evidence for this widely publicized assertion.

No convincing data yet exist to demonstrate that most medical and public health students now devote the same amount of time learning the basic sciences, or reading the current medical literature, as when such learning was required by the classroom instructors. There is also little doubt that many students, like the general public, accept what they read on the computer as factually correct, and that examinations are now based more on easily manipulatable computer output than on the substance of medical textbooks and the peer-reviewed medical literature. In earlier decades, most medical students attended class and laboratories six days a week. One might wonder how today's students can achieve an acceptable level of knowledge about a massively larger body of medical science than in the past, with so much less time being spent in the classroom, laboratory, or examining patients.

We have noted that classical clinical and basic medical science research in preventive medicine departments and public health schools has declined in recent decades, along with hypothesis-based studies, as the classrooms and laboratories are now largely depleted of physicians and nurses with clinical or research training. Their replacements are social scientists who are primarily interested in social, behavioral, psychological, economic, and other subjects of value that are remote from traditional avenues of medical

science. Biostatisticians, who in earlier eras worked closely with medically trained epidemiologists in studies such as those presented in this volume, have readapted their skills to new niches in the public health arena, viz. applying their techniques to social and behavioral research, and providing biostatistical support for the enormous increase in computer-based genetic studies. A large number of theses and publications continue to count cases of disease rather than trying to understand their etiology. And, as in the past, there is no shortage of studies focusing on trivial observations, which cannot be causal or otherwise significant. It may also be of note that the number of personnel devoted solely to diversity issues is the fastest growing division within many medical and public health schools.

BIG DATA VERSUS EPIDEMIOLOGY

A dramatic result of the changes undergone by the preventive medicine departments and public health schools has been a rapid decline in clinically trained physicians, dentists, veterinarians, and nurses applying for admission as students, and seeking careers in classical epidemiological teaching and research. Remedial courses in clinical and basic medical science have been offered to the largely non-medical student bodies now enrolled, but neither students nor faculty believe that these casual lectures can substitute for the traditional course offerings. Another consequence has been an increased level of uneasiness between (a) the shrinking minority of medically trained faculty and students and (b) the growing majority of social science faculty and students. Now that a new status quo has been established, with a clear majority of nonclinical faculty and trainees, the tension has begun to dissipate, but the paucity of epidemiologic opportunities for the clinically prepared students continues to be ignored.

Many studies these days utilize data from previously published research or from unpublished data collected for other purposes, to initiate what are often called "new" studies. For example, rather than designing a project on the effect of smoking, gender, or other host factors on the risk of a disease by careful selection of a patient sample, follow-up of cases, and a representative control group, and comparing the disease risks, the investigators now feed their "previously published for another purpose" data into a computer and generate estimates of interaction between the host factors and their disease of interest. Such studies lack the integrity of truly "new" studies designed by epidemiologists following the traditional procedures.

There are philosophical and practical distinctions between "Big Data" and the classical epidemiological approaches. The Big Data approach seems to violate some basic rules of science and logic:

1. **Analyzing data not designed for the express purpose of a specific study is highly likely to yield erroneous results**. Whom do the patients in such studies represent? Is the control population in these studies representative of a universe of patients without the disease or factor of interest, as required in traditional scientific investigations?
2. **Since Big Data studies are not designed de novo by the investigator, the host factors of interest will not have been collected from the subjects with the same care and intensity as in classical studies** which specify that these factors are central to the study. Some supporters of Big Data seem to believe that such problems can be avoided by simply increasing the volume of patient data fed into the computer. Such a

theory would hold only if the patient group were truly representative of a real universe of patients with the predefined characteristics of interest.

3. **The Big Data system is a type of fishing expedition employing the computer**. If a study is undertaken without specifying a hypothesis, it may live up to its promoters as a novel approach to advancing knowledge independently of biological and statistical reasoning. But it can succeed only if the numbers of patients and their characteristics of interest begin to approximate those of a "universe" to which the study can be designed to represent. Otherwise, it is an expensive data processing exercise, the results of which cannot be generalized to any specific real-life population at risk.
4. **Biologic truth and statistical analysis may be irreconcilable**, if the latter is applied post hoc to biologic data of a patient population previously selected for a totally different research purpose.
5. **The Big Data approach to investigating risk factors in the pathogenesis of disease is usually a sequence of (a) ignoring hypothesis formulation; (b) ignoring precise selection of patients and controls; (c) avoiding biological reasoning; (d) misusing statistical reasoning; and (e) limiting the analysis to the variables found in the Big Data set that may be of little pertinence to the investigator.**

Traditional studies of human subjects undertaken to advance knowledge about health and disease usually fall into one of the following categories, in which Big Data can play no role:

1. **Uncontrolled clinical observations** on people considered by physicians or others to be ill or healthy at

the time and deemed significant enough to be recorded. Such studies, undertaken for thousands of years, sometimes lead to valid conclusions about a disease or risk factor, but usually do not.

2. **Uncontrolled population studies** lacking hypotheses. Examples include analysis of time trends in cancer admissions at a hospital, or occurrence of a risk factor among occupational groups. Conclusions are mostly unverifiable.
3. **Routinely collected death certificate data**. Conclusions are usually unverifiable.
4. **Correlational studies** (e.g. lung cancers and smoking have both increased over time, suggesting that smoking may be a causal factor; but many other totally unrelated environmental and behavioral factors have also become more prominent over time, demonstrating the weakness of such research). Most conclusions from such studies are unverifiable.
5. **Controlled studies of the case–control type, involving cases with, and controls without, a disease or factor under study**, usually undertaken with a testable hypothesis (e.g. bladder cancer cases compared to disease-free controls, studied for saccharin exposure or herpesvirus antibodies). The strengths of this approach include controlling for confounding variables; the relative simplicity of conducting the study; and the limited time required to complete the study. The weaknesses include possible bias in assessing exposures to a disease factor many years before the study; controls selected from hospital or other sources may be inappropriate; difficulties in selecting representative controls; and reliance on measurements of relative risk, rather than true risk.

6. **Controlled cohort or prospective studies** (e.g. risk of cancer in appendectomized or tuberculous- or DES-exposed patients and controls). The strengths of this approach include the absence of bias in assessing exposure to the risk factor; measurement of the true risks of exposure; and multiple outcome factors may be measured at little extra cost. However, follow-up is prolonged, expensive, and often difficult. Prospective studies conducted in retrospect, i.e. long after exposure to the risk factor, are also feasible; they have technical advantages but are rarely undertaken these days.
7. **Experimental studies or randomized trials** [(e.g. a polio vaccine trial in young children, half given the vaccine and half not, followed for the incidence of polio; or a randomized cohort of male volunteers, half initiating a cholesterol-lowering diet and half not, followed for five years to observe the incidence of myocardial infarction).] Such trials are a gold standard of epidemiologic research, despite their inherent difficulties.

SIGNIFICANCE OF CONTROLS

A brief discussion on the importance of properly selecting cases and controls for human studies may be useful here. **Cases are often difficult to define with precision**. For example, a diabetic patient may be newly diagnosed or the survivor of many years with the disease. The type of diabetes may vary, and insulin may or may not be required. A patient with Parkinson's disease can be variable in regard to a host of observed characteristics and, in addition, may lack any or most of the classical diagnostic criteria of the disease. Arthritis, in its many forms, is another example of the

difficulties in defining a disease to be studied with epidemiological rigor.

Most epidemiological studies of the case–control variety are based on patients drawn from hospital inpatient and outpatient sources, because of the ready availability of cases, simplicity of selecting controls, and easily obtained ancillary medical data. A single hospital, multiple hospitals, or a statistical sampling of hospitals regionally or nationally may be selected for study. When non-hospitalized cases and controls are studied, the issue of whether such patients differ from hospital-based patients in respect to the outcome variables may be raised. Which group better represents the newly diagnosed cases or the prevalent cases? Which are likely to have received a more valid diagnosis of the disease of interest?

Other patient data often studied includes records of published health studies, and subjects selected from insurance company lists or death certificates, although such compilations are not designed specifically for epidemiologic study, and are replete with data flaws that cannot be remediated.

Household-type surveys, if representativeness can be achieved, are another scientifically valid method of securing cases and controls for study, although the costs and complexity of this approach are well established.

The importance of properly selecting controls is often minimized, or even ignored, by many in the bioscientific community. Advertisements to recruit cases and controls are now commonly posted on bulletin boards in newspapers, schools, universities, grocers, and coffee shops. Payments to

patients are now commonplace among researchers and medical school sponsors. One may wonder about the respondents to such crass solicitations. Are they primarily individuals concerned with their disease, or those eager to earn a few dollars? Or do they have another motivation to participate? The bottom line is that **the cases must represent the universe of patients with the disease, and the controls must represent the universe of those without the disease, so that an appropriate statistical test may validly differentiate between them in the selected universe**. This epidemiological principle, once universally accepted in the world of medical research and education, has lost much of its credibility and many of its traditional adherents.

Subjects selected as controls must, of course, lack the disease or risk factor of interest, but should closely resemble the cases in many other ways, in order to reduce possibly significant differences between them. Their sex, race, and age should not differ from that in the cases because such characteristics are often related to the clinical manifestations of the disease or risk factor, either directly or indirectly. Using variables such as the particular hospital involved admission date, marital status, or a measure of socioeconomic status may strengthen the likelihood of finding meaningful case–control differences. Statistically matching individual pairs or groups of cases and controls eliminates the effects of the matched variables on the study outcome. And the participation rates of patients in all these studies should be as high as possible, among both cases and controls.

The advantages of selecting a case–control approach over a prospective design include: (1) a lower cost; (2) smaller number of subjects required; (3) results obtainable in the shortest time span; and (*4*) style *most suitable for studies of*

rare diseases. The disadvantages include: (1) a history of past exposure to the risk factor may be unavailable or flawed; (2) biased reporting of risk factors is more likely [(e.g. a smoking habit prior to cancer)]; (3) increased complexity of assembling appropriate control groups (e.g. hospital or clinic controls have a Berksonian type of selection bias, where the disease responsible for their hospitalization may affect a number of traits among the controls); and (4) this approach measures relative risk but not true risk.

MEASURING VALIDITY OF RESEARCH

The **validity** of a study's outcome should be measured by its (1) **sensitivity** (extent to which patients with the characteristic of interest are correctly classified); (2) **specificity** (extent to which the patients without the characteristic of interest are correctly classified); and (*3*) **predictive value** [(extent to which the patients classified as positive are truly positive]).

True causality in epidemiological studies is inferred, not primarily from statistical tests, but from biological data interpreted epidemiologically, as may be seen in the following types of observation:

1. **Coherence** of the test findings with valid existing biomedical facts about the disease.
2. **Consistency** of the test findings in multiple studies.
3. **Dose–response effects**, demonstrating a higher risk of disease with an increase in the strength or quantitative exposure to the risk factor.
4. **Increased relative risk of disease** among patients exposed to the risk factor.
5. **Other causal findings requiring special attention**: when the slope of the dose–response is gradual rather

than clear-cut; when there is no apparent threshold dose of the factor required to produce the biological effect; and when the maximum-tolerated dose of the test factor approaches potentially hazardous, or even lethal, levels in the animal or human subjects.

6. **Animal and tissue culture findings** from animal-based studies that are biologically consistent with a causal effect.

The role of the statistician in medical science evolved in a rather unusual fashion over the past century. Statistical proofs of causality were coming into fashion in the early 1900s and, over a few decades, became a near-final step in most researchers' investigations. Biological and epidemiological reasoning continued to be involved, although their influence gradually diminished with the advent and flourishing of the computer which reduced the researcher's role. The fact that most biomedical faculty and student bodies are insufficiently trained in statistics—at a time when this discipline has become unusually influential in medicine—is another complicating issue. How many bioscientists now realize that there are assumptions underlying the valid application of every statistical test, which must be satisfied before it is legitimately employed? For example, is the distribution of a data set "normal," "logarithmic," "Poisson," or other? Statistical packages, which are widely used, do not automatically check assumptions of linearity, independence, or homoscedasticity, for example.

The arrival of the Big Data approach hastened the demise of hypothesis formulation in biomedical research, so that more and more bioscientists and epidemiologists are tending to wait for their Big Data computer output to dictate what should be done next. A serious consequence of this process is that

statistical reasoning dominates, while biological and epidemiological reasoning are diminished, in graduate student and professorial studies that emphasize quantitative analysis of genome arrays. The watered-down basic science curriculum in medical and public health schools, the disappearance of classical epidemiological studies of agents, hosts, and environments of disease, and the tendency of students to be guided by mentors who are busy pursuing their own careers offer little hope for effective change.

Medical research in the United States has a long and distinguished history of excellence and, for many years, was recognized as the leading enterprise of its type in the world. Assessing whether and how this relative superiority has changed over time is difficult, since it depends on objectively comparing the conditions and methods of current research with the earlier efforts. As described above, research in earlier times usually began with the development and refinement of ideas into testable hypotheses. Previous studies of a disease would be meticulously reviewed and a proposal would be created, e.g. identifying a possible causal factor in the pathogenesis of the disease. This would be followed by developing a research proposal, stating a specific hypothesis, refining it, and finally submitting an application to a bona fide funding agency. As mentioned above, it is our impression that hypothesis-testing proposals and studies involving serious applications of epidemiologic reasoning are gradually disappearing from our medical and public health schools at a time of enhanced interest in genome-based investigations. This issue, and the future roles of public health schools and preventive medicine departments, are discussed in the final chapter of this book (Chapter 19).

CHAPTER THREE SUMMARY

CANCER RISK AMONG DIABETICS

Coincident cases of cancer and diabetes mellitus have been reported for well over 100 years. In the early 1920s, a series of studies led to the discovery and crystallization of insulin, and to observations on metabolic differences between normal and malignant tissue. The comparable effects of certain tumor tissues and insulin on glucose utilization and lactate production suggest the possibility of a biologic relationship between cancer and the newly identified pancreatic hormone. The "riddle of tumor hypoglycemia" has persisted, even as attention moved from glucose oxidation to broader areas of inquiry. It has been proposed that genetic or virus-induced mutations in the mitochondria derange the hexokinase phosphorylating system leading to glycolytic dysfunction. Studies also suggest that a mutagenic effect of diabetes expresses itself either in teratogenesis or carcinogenesis, while other findings support the view that diabetes and cancer are related through competitive abnormalities in fat metabolism rather than defects in glycolysis or nucleic acid synthesis.

Our epidemiological study of the diabetes–cancer relationship evaluated cancer risk in a large population of diabetics examined at the Joslin Clinic, a renowned diabetes clinic located a few blocks from the Harvard Medical School. The target population was diabetic patients seen between January 1930 and July 1956 who survived for at least one year beyond

their first clinic visit. Their risk of death from cancer of any type was compared to that of the Massachusetts population subclassified by age, race, and sex.

The findings included a significantly increased risk of pancreatic cancer among all diabetics, and a reduced risk of cancer of all types combined among male diabetics. Playing possible roles here are competitive risks of death from coronary heart disease; the greater percentage of Jewish patients and patients of Russian origin in the Joslin population than in the state; and a possible X-linked recessive genetic trait, in which increased susceptibility to diabetes is associated with a decreased susceptibility to cancer.

CHAPTER THREE

CANCER RISK AMONG DIABETICS

BACKGROUND

Coincident cases of cancer and diabetes mellitus have been reported in the medical literature for more than a century. Until World War I, many investigators, intrigued by the hyperglycemia in certain cancer patients, suggested that blood-sugar measurements might serve as a screening or diagnostic test for cancer. Interest in this grew with the development of the glucose tolerance test, but then faded as evidence for unique glucose tolerance curves in cancer patients was not forthcoming.

In the early 1920s, research entered a new phase with the discovery and crystallization of insulin, and with observations on metabolic differences between normal and malignant tissues. The comparable effects of certain tumor tissues and insulin on glucose utilization and lactate production focused attention on the possibility of a biological relationship between cancer and the newly identified pancreatic hormone. The presence of assayable insulin in many normal and diabetic human tissues was followed by studies of extra-pancreatic insulin elaboration in human and animal tumors. Operating to confound these relationships, however, was the action of the pituitary and other endocrine glands in regulating blood sugar as well as other aspects of carbohydrate metabolism.

The “riddle of tumor hypoglycemia” continued, as the focus of attention shifted from glucose oxidation per se to broader areas of inquiry. Deoxyribonucleic acid was identified as an important constituent of the insulin-like extracts from various rodent tumors, suggesting that the observed relationship between normal or abnormal carbohydrate metabolism and cancer results from a relationship with nucleic acid or nucleoprotein synthesis. The anatomical site for this relationship could be the mitochondrion, which is known to be active in cellular respiration. A schema was proposed that postulated genetic or virus-induced mutations in the mitochondria, leading to derangement of the hexokinase phosphorylating system and, in turn, to glycolytic dysfunction.

Other studies suggested a relationship between cancer and diabetes, but only hinted at an underlying mechanism. Exogenous insulin induced carcinogenesis in hypophysectomized rats fed an otherwise ineffective dose of 3’-methyl-4-dimethylaminoazobenzene. Mouse mammary adenocarcinomas seemed to lose their requirement for insulin, and glycosuria was suppressed in diabetic rats implanted with tumor tissue. Insulin antagonism is significantly elevated in the mothers of children with congenital anomalies, suggesting that a mutagenic effect of diabetes may express itself either in teratogenesis or carcinogenesis. Another study suggested that diabetes and cancer are related through common or competitive abnormalities in fat metabolism, rather than through defects in glycolysis or nucleic acid synthesis.

DESIGN

We decided to recruit a large population of primarily white diabetics who had undergone examination at the Joslin Clinic, a famous diabetes clinic located a few blocks from the

Harvard Medical School. The totality of Joslin Clinic patients seen between January 1930 and July 1956, and who survived for at least one year beyond the date of their first visit, became the target population. Only 0.7% of this cohort was lost to observation while still alive before January 1, 1960, the study termination date. The study population was a retrospective cohort of diabetics who visited the clinic and were followed to death or survival as of a later point in time. The cohort's risk of death from cancer was compared to the experience of the Massachusetts population.

Patients seen at the Joslin Clinic before June 1939 were classified as diabetic if their "venous blood sugar on an unrestricted diet was 130 milligrams percent or more fasting, or 170 milligrams percent or more after a meal, with a simultaneous glycosuria plainly related to diet". For practical reasons, it was not possible for us to review the death certificates of all 10,066 diabetics who died during the study period. Instead, clinic records were used to identify the patients who had died of cancer. Analysis of a random 25% sample of the population whose death certificates were reviewed revealed that only 1.9% of the cancer deaths among males and 2.9% of those among females had been missed by the procedure employed (Kessler 1969,151-152; Kessler 1971a, 715-724).

In the analysis of deaths from specific causes, the underlying cause coded on the death certificate was used. If the certificate lacked a coded cause, this was supplied after reference to the International List of Causes of Death and, if necessary, to the Manual of Joint Causes of Death current at the time of death. The observed number of deaths from each cause was compared with the expected number, taking into consideration the person-years of exposure to the risk of death.

ANALYSIS

Age- and sex-specific annual numbers of deaths (by 10-year age group) from each cause were abstracted from the "Annual Report on the Vital Statistics of Massachusetts." The annual cause-specific death totals were combined to give totals for each of six time periods for which intercensal population estimates had been calculated. The periodic death totals were then divided by the respective intercensal population estimates to yield six age- and sex-specific expected death rates. Multiplying each expected death rate by the respective age- and sex-specific person-years of observation undergone by the study population since their initial clinic visit yielded, after summing, the expected number of deaths from each given cause. Standardized mortality ratios (SMRs) were computed by dividing expected numbers of deaths from each cause into observed numbers, specific for each sex and time period.

A chi-square statistic was used to test for the significance of each SMR deviation from its null value, 1. The statistic employed was based solely on the deviation of the observed number of study population deaths from the expected value. Since deviation of observed non-deaths from their expected value would contribute insignificantly to this statistic, it was ignored and thus made the statistic somewhat more conservative, i.e. less likely to attain a significant value. The manner in which the expected number of deaths was calculated (viz. from a series of death rates, rather than from a single rate) probably had a similar effect.

Observed deaths from cancer of all types combined among male patients were significantly below the expected number: 358 versus 421 ($P<0.005$). The 544 deaths among females exceeded the 530 deaths expected, but not significantly so.

Correction of the observed numbers by addition of the 7 male and 16 female cancer deaths, estimated on the basis of the 35% sample to have been missed, had no substantial effect on these relationships (Kessler 1970a, 673-686).

Among the male diabetics of all ages, observed cancer deaths fell below their expected number during each time period. The largest apparent deficit of cancer deaths occurred from 1951 to 1959, but no clear-cut trend in cancer mortality was discernable. Examination of the mortality pattern by age over the entire observation period revealed a deficiency in male cancer deaths among all groups above age 44, except for the 55–59 age group. The diminished mortality was also observed when individual time periods were examined. Observed and expected numbers of cases among males below age 40 were too small for reliable comparisons. When the diabetics were grouped into 10-year age classes, their SMRs during each period decreased, mainly among men aged 60 and over. In females, the mortality pattern differed considerably from that among males. Observed cancer deaths exceeded the expected number during three time periods and fell below during three others, with no apparent trend over time.

Among the 15 specific types of cancer examined, statistically significant excess in deaths was observed only for cancer of the pancreas. In males, 30 deaths were observed against 20 expected [($P<0.05$]); in females, 48 deaths were observed against 23 expected [($P<0.001$]). The two deaths [1 in each sex] estimated to have been missed were too few to affect this mortality pattern. During each time period, observed pancreatic cancer deaths among females exceeded their expected number; among males this was also true, except for the period 1956–-59. Less than 1 pancreatic cancer death was expected for all age groups under 50 in males and under 55 in

females during the entire observation period. If these age groups are ignored, and observed and expected numbers of deaths are calculated for the patients of older ages, an excess mortality from pancreatic cancer was observed in all 10-year age groups among males, and in all but the oldest age group in females.

There were 44 deaths from cancer of the uterus observed and 61 were expected, a difference that was highly significant ($P<0.001$). A deficiency of deaths was found in all time periods except the first, as well as in most age groups over the period of study. Only one age group (80+) deviated substantially from this pattern. Mortality from cancer of the uterine cervix could be examined only for the years from 1940, when it began to be coded separately from uterine cancer in US vital statistics registries. There were 14 deaths observed and 21 were expected, a difference that was not statistically significant ($P>0.05$). However, a highly significant deficit was observed from 1941 to 1959 in the number of deaths from uterine cancer exclusive of cervical cancer. There were 19 deaths observed against 30.7 expected, a finding that would rarely occur by chance ($P<0.25$). This deficiency was noted in each of the four time periods and among all age groups except the oldest.

For all other cancers, none revealed statistically significant mortality risks in the diabetics, either male or female. Stomach and bladder cancer in both sexes, and Hodgkin's disease, breast cancer, and cervix cancer in females occurred with frequencies reduced by 10% or more below expectation. However, none of these cancers showed any consistent pattern of reduced risk over age or time.

By comparing the diabetes onset date with the death certificate statement on cancer onset or duration, it was possible to estimate the proportion of cancer decedents in whom diabetes preceded cancer. Among 267 male and 436 female cancer decedents, information was sufficient in both clinic records and death certificates to determine which disease occurred first. Diabetes was first in 98% of the males and 94% of the females. However, 199 cases lacked enough data to permit a judgment.

Diabetes mellitus preceded cancer in most patients who died of pancreatic cancer. This was unequivocally true in 22 of the 30 males and 33 of the 48 females, whose mean survival after diabetes onset was 11.4 +/- 2.9 years. Cancer onset occurred within 1 year of diabetes onset in 2 males and 5 females. While the date of cancer onset could not be determined for the remaining 16 patients, survival after diabetes onset was 12 years or more for 7 of them, 6 years or more for 11, and 1.3–4 years for 3. There were 4 males and 7 females whose cancer onset was judged to have occurred before the first anniversary of their first clinic visit. If these deaths were excluded from the observed number, the SMR in males fell to 1.27 and ceased to be statistically significant ($P>0.300$). However, the female SMR (1.82) remained significantly increased ($P<0.001$).

The study population's risk of death from all causes combined and from causes other than cancer was estimated from the experience of the 25% sample. The diabetics had a risk of death from all causes, which exceeded expectation by 64% among males and 122% among females. Most of the excess was accounted for by diabetes mellitus, with an additional contribution by coronary heart disease. When these two diseases were eliminated as causes of death, the total

mortality risk among diabetics ceased to be significantly increased, though it remained elevated at a marginal level of statistical significance among females (Kessler 1970a, 673-686).

DISCUSSION

The results of this study suggest that male diabetics may have a significantly reduced risk of death from cancer of all types combined. The consistency of this finding over age and time lends it credence: cancer mortality among the diabetic males fell below expected levels during each of six time periods and in most of the age groups examined, though the differences were often small. But among females, observed cancer deaths approximated their expected numbers in total, with no consistent trends over time or age.

To judge by the calculated SMRs, cancer risk among male diabetics was about 15% lower than that in the general population over the entire period of study and 20% lower since 1950. Among US whites in 1950–51, the age-adjusted total cancer death rate was 12% higher among males than females. For the 24 countries examined by Segi and Kurihara (1963), the age-adjusted total cancer death rate in 1950–51 averaged 16% higher in males than in females.

One may consider the possibility that the reduced cancer risk among male diabetics is related to the process that accounts for the excess of male cancer deaths seen in most general populations. In other words, the sex difference in the cancer risk of diabetics may reflect an aspect of the relationship between the two diseases. Possibly only one or a few specific neoplasms are associated with diabetes in this manner. The highly significant sex-specific reduction in respiratory cancer

mortality among male diabetics suggests that the negative association exists specifically between diabetes and lung cancer. However, this cannot account for all of the reduced cancer risk in male diabetics.

To explain the reduced cancer risk among male diabetics, one must consider the competitive risks of death to which the patients were subjected. Diabetes mellitus and coronary heart disease accounted for all the excess mortality of the male diabetics. Among the females, however, the mortality remained excessive at a marginal level of statistical significance, even after these two causes of death were excluded. Thus, the deaths from diabetes and coronary heart disease appear to have affected the males disproportionately. The excess risk of death from these two causes may have competed with, and reduced, the apparent risk of death from all other causes, including cancer. If real, this effect would have been enhanced by the advantage that male diabetics hold over females in overall survivorship relative to that of the general population. A greater survivorship would imply relatively reduced probabilities of death from all other causes.

If competitive risks explain the sex difference in cancer mortality, then one would expect to find this reflected in the manner in which the relative risks of death from cancer, diabetes, and coronary heart disease varied over time in both sexes. The relative mortality from coronary heart disease among males was maximal during 1951 to 1959, which was the period of minimal risk of death from both cancer and diabetes. Among females, however, the excess mortality from all three diseases peaked simultaneously (1956–59). Thus, the observed sex difference in cancer mortality among diabetics is consistent with a competitive risk model in males, but not in females.

One possibly significant finding was an over-representation in the study population by Jewish patients. While 17% of the diabetic group were Jewish, the proportion of Jews in Massachusetts during the study years was less than 5%. This difference was probably due to three factors: (a) the higher incidence of diabetes among Jews; (b) a greater prevalence of recognized diabetes among Jews due to their higher socioeconomic standing; and (c) the one-year survivorship eligibility criterion, the application of which excluded relatively fewer Jews than non-Jews.

Data from two recent studies indicate that cancer mortality in Jewish males tends to be lower than that in Catholics or Protestants, while the reverse is true for Jewish females. King, Diamond, and Bailar (1965, 349-358*)* computed cancer mortality differentials by religious affiliation, expressed as ratios of age-adjusted death rates to the corresponding rates for all faiths combined. Newill (1961, 495-417) calculated average annual cancer death rates per 100,000 among New York City whites aged 45 and over in 1953–58 under the assumption that age variation in the religious distribution could be safely discounted after age 45. None of these authors computed probabilities for these figures or for the significance of differences between the figures. However, the two studies consistently demonstrate a relatively reduced cancer risk among Jewish males, contrasted with an increased cancer risk among Jewish females. The question remaining is whether the sex difference in diabetic cancer mortality is related to the overly represented Jewish patients.

When the findings of this study are compared to those of King et al. (1965, 349-358*)* and Newill (1961, 495-417), diabetics and Jews show a high degree of concordance in their risks of death from most types of cancer. This is especially

noteworthy in respiratory cancer, for which both diabetics and Jews experience diminished risks among males and enhanced risks in females. The mortality of the two groups differs principally for neoplasms of the reproductive organs and the stomach. Among Jews, cancers of the breast, ovary, uterine corpus, and stomach tend to be high, and prostate cancer tends to be low. Not only does the experience of the diabetic group differ, but the Jewish diabetics also had an even smaller relative risk of death from breast and prostate cancer, if the small numbers on which these observations were based can be ignored. In any event, it appears that, except for neoplasms of the stomach and reproductive organs, diabetics and Jews have a similar pattern of cancer risks.

In addition to its over-representation of Jews, the study population had an unexpectedly high proportion of Russian-born patients, most of whom were also Jewish. Comparison with the data of Haenszel (1961, 37-132) on the cancer mortality of Russian-born Americans indicates that the pattern of cancer risks in diabetics bears little resemblance to that of Russian-born immigrants. In particular, the latter show no sex differentials in mortality from either total cancer or respiratory cancer. Apparently, the observed cancer mortality of the study population was influenced far more by its Jewish, rather than Russian, composition.

The relative risk of cancer among Jews almost certainly is not so different from that of non-Jews that a diabetic population of 17% Jews would have its cancer mortality reduced by 15%. It is therefore pertinent to ask, not whether the cancer risk of diabetics is affected by the presence of Jews but, rather, whether the cancer risk of Jews is influenced by some factor held in common with some, or perhaps, all diabetics. Such a factor could be environmental, e.g. a low frequency of

cigarette smoking, which could account for the reduced respiratory cancer risk among both diabetic and Jewish males. Of course, this model would not be consistent with the significantly elevated coronary heart disease mortality found among diabetics of both sexes.

A constitutional or genetic factor is another possibility. An X-linked recessive genetic trait, in which increased susceptibility to diabetes was associated with decreased susceptibility to cancer, could account for a negative association between diabetes and cancer in one sex alone. The survival value of such an as yet unidentified genotype to the diabetes gene(s) in a population would be considerable, particularly if reduced risks of childhood neoplasms were involved (Kessler 1970b, 218-220).

A definitive finding in this study was the significantly increased risk of death from pancreatic cancer among diabetics. The magnitude of the relative risk may be seen in perspective if one notes that the SMRs were approximately equal to those for coronary heart disease, which is generally believed to be associated with diabetes. The consistency of these findings over age and time in both sexes was impressive.

Because these tumors might be expected, a priori, to show associated abnormalities in carbohydrate metabolism, it is especially important with pancreatic cancer to establish that diabetes was the antecedent disease. This cannot be done with absolute certainty because there is no known method to identify small, asymptomatic pancreatic neoplasms, which (at least, theoretically) could produce symptoms of diabetes long before those of cancer.

The eligibility criterion of one year's survival after the first clinic visit must have greatly reduced, if not eliminated, cases in which pancreatic cancer was antecedent. This is so because survival beyond a year with known pancreatic cancer is unusual. Conversely, the fact that more pancreatic cancers than any other cancers were excluded by this criterion may arouse suspicion that diabetic symptoms are a prodrome of the neoplasm. In addition, the interval between first clinic visit and cancer onset was less than 1 year for 11 of the 78 decedents from this cause: 4 of the 30 males and 7 of the 48 females. Possibly, in some of these cases, the cancer preceded the diabetes.

Because the SMR computed for males was 1.47 (compared with 2.13 for females), any attempt to eliminate deaths because of a suspicion that the cancer may have antedated the diabetes would affect the findings for males more than for females. In other words, the evidence that diabetics are at a high subsequent risk of death from pancreatic cancer is stronger for females than for males.

The same sex differential in pancreatic cancer risk was observed among the Jewish diabetics: 4 deaths in males compared with 3.69 expected, and 10 deaths in females compared with 3.34 expected. Newill (1961) found a greater risk of pancreatic cancer mortality among Jews than non-Jews in New York City, and his figures indicated that the excess risk was nearly twice as high in females (27%) as in males (15%).

Pathological studies show a stepwise increase in the prevalence of pancreatic duct hyperplasia, as normal tissues progress to those of diabetics and thence to those of pancreatic cancer patients. Such a pattern is consistent with

the possibility that the two diseases share an etiological factor. The genetic hypothesis suggested above is compatible with the operation of an environmental agent as well.

That pancreatic cancer—of all cancers—exhibits a uniquely strong association with preexistent diabetes, at least among females, suggests that the hypothesized environmental carcinogen might be specifically related to pancreatic tissue. Exogenous bovine or porcine insulin comes immediately to mind. These substances are teratogenic and antigenic in laboratory animals, though there is no evidence at present of their carcinogenicity in humans. A study of this question is needed. This might take the form of an analysis of the pancreatic cancer risk among patients with diabetes of comparable severity, who are under various therapeutic regimens including insulin (of both beef and pork origin), oral hypoglycemic agents, dietary management, and combined therapy.

The expected male preponderance in the risk of death from lung cancer was considerably reduced among the diabetics. This was due mainly to a relative decline in risk among males, which first appeared around 1941 and became increasingly prominent thereafter. The risk among female diabetics remained somewhat higher than among females generally, except for the 1951–55 period. Correcting for presumably missing and non-pulmonary cases served to accentuate the male–female differential.

The differential was also accentuated among the Jewish diabetics, a finding consistent with that of Newill (1961, 405-417) and King et al. (1965, 349-358) in their studies of cancer in Jews, Catholics, and Protestants. Horowitz and Enterline (1970, 275-282) reported that epidermoid lung cancer, the

type usually associated with smoking, is particularly infrequent among Jewish males. Since perhaps 90% of lung cancers are attributable to cigarette smoking, one is probably justified in inferring from all the above that male diabetics (especially Jews) smoke less frequently than others. Consistent with this view is the suggestion of a significant reduction in male deaths from respiratory disease. Unfortunately, no data on this issue can be found in the current literature.

Although differential smoking habits reasonably explain the observed pattern of lung cancer mortality in diabetics, one must still account for certain other, possibly contradictory, findings. If, for example, infrequent smoking protects male diabetics from lung cancer, why should they be so singularly unprotected from the risk of coronary heart disease, also associated with smoking? The answer probably lies in the much stronger association existing between diabetes and coronary heart disease than between smoking and coronary heart disease.

If there is any validity to the previously discussed genetic hypothesis for the sex differences in cancer risk, then these findings on lung cancer mortality may not be attributable solely to differences in smoking habit. The question could be resolved by an investigation of smoking patterns in diabetics and non-diabetics, stratified by sex and religion.

Deaths from all cancers of the uterus combined were reduced significantly among the female diabetics. Both Newill (1961, 405-417) and King et al. (1965, 349-358) found Jews to have substantially lower death rates than non-Jews from cancers of the uterus. Corpus and cervix neoplasms differ markedly in their epidemiological correlations, and the risks for each type should be examined separately. Nevertheless, the close

resemblance of diabetics and Jews in their overall mortality from uterine cancer remains of interest.

The observed low SMR for cervical cancer during 1940 to 1949, though not statistically significant, would be expected for a middle-class group, especially one over-represented by Jews. For the same reason, the decreased SMR for corpus cancer after 1940, even though statistically insignificant, was unexpected. The number of observed deaths over most time and age classes was consistently below expected levels.

Differential survival rates from corpus cancer represent one possible explanation if, by virtue of readier access to medical care, the diabetics experienced a lower fatality rate than the general population. But there is no evidence presently favoring this view. In fact, some existing evidence is to the contrary. Andersen (1952, 178-182) observed that radium-resistant endometrial tumors are associated with impaired glucose tolerance. Patients with such tumors would be expected to show the poorest survival. In studies of gynecological clinic patients, Bach and Stegmann concluded that the frequency of complications and mortality among diabetic patients with endometrial cancer was considerably greater than that among non-diabetics (Kessler 1971b, 579-600).

Recently, a consensus appears to have arisen among many clinicians that diabetes is more prevalent among patients with endometrial cancer. This conclusion does not agree with the findings in our study population, and differences in methodology are probably responsible. In the present study, the antecedence of diabetes to cancer could be established with relative ease in most cases. In contrast, the clinical studies cited usually involved retrospective inquiry into the

diabetes status of the cancer patients. Cancer could have been the antecedent disease in a significant portion of patients in these studies. In any event, an investigation into the incidence of cancer among diabetics, rather than its mortality, would help resolve the question (Kessler 1970b, 218-220). The Maryland Cancer Registry, had it survived intact, would have been a most appropriate database for such a study [Chapter 10].

CHAPTER FOUR SUMMARY

PARKINSON'S DISEASE: ROLES OF MELANIN AND NICOTINE

Tremors have been observed and explored for two millennia, since Galen's text on "De Tremore" classified these neurological manifestations into voluntary, involuntary, and other movements. Nothing new emerged about the disease until 1817 when James Parkinson published "An Essay on the Shaking Palsy" and labelled the condition "paralysis agitans." The disease was later renamed Parkinson's disease in his honor. Like Ramazzini and other epidemiologically oriented physicians of his time, Parkinson described patients who demonstrated similar neurological symptoms during his daily perambulations, as well as their comments to him. His clinical observations and epidemiological conclusions were as precise as any well-trained physician could achieve today, lacking only critical medical information and diagnostic findings that accumulated since his time.

A dilemma in studying Parkinson's disease is that some of the diagnostic criteria, including bradykinesia, rigidity, resting tremor, postural instability, and response to levodopa, may or may not be present in every patient. It was also of interest to me whether the known neuropathological effects of nicotine might play an etiological role in this disease.

We undertook two investigations: a **hospital-based study** consisting of a random sample of all hospitalized patients in

Baltimore who were diagnosed as having Parkinson's disease during a three-year period of time, and a **community-based study** of a stratified random sample of Baltimore physicians and their Parkinson's disease patients. Both studies revealed that black patients were at a lower risk of the disease, a finding that is probably biological rather than linked to inadequate medical care or misdiagnosis. The studies also demonstrated that the disease risk among black patients declined with increasing use of tobacco. This finding is significant because nicotine has a strong relationship with the central nervous system, and because black patients are more heavily endowed with melanin in and around the basal ganglia. Our results led a number of hospitals to undertake nicotine treatment trials for Parkinsonism, yielding some positive results.

CHAPTER FOUR

PARKINSON'S DISEASE: ROLES OF MELANIN AND NICOTINE

BACKGROUND

Tremors in patients have been observed for over two millennia, since Galen's text on "De Tremore" classified such neurological manifestations into voluntary, involuntary, and other movements. Nothing else emerged about the disease until 1817 when James Parkinson, a London surgeon with a lifelong interest in fossils and a strong advocate for the underprivileged, published "An Essay on the Shaking Palsy" and named the condition "paralysis agitans." The disease was later renamed Parkinson's disease in his honor by a later investigator, Jean-Martin Charcot.

Like Ramazzini and other physicians of his time, Parkinson described patients who shared the symptoms of neurological disease, based on his observations and conversations with them during his daily walks. But it must be remembered that no diagnostic criteria for Parkinson's disease had been established, nor were any neurological examination criteria yet developed. Parkinson's 66-page volume described cases of varying severity, and his astute clinical observations were the first to focus attention on the disease's insidious onset, long duration, asymmetry of motor signs, tremor at rest, sense of weakness, flexed posture, and festinating gait.

The relatively small number of cases he studied were so diverse that Parkinson was also able to observe that the disease was progressive, led to immobility and dependence increasing over time, and had long-term complications such as disturbances of sleep, speech, and bodily functions, while, at the same time, leaving the senses and intellect unimpaired. His review of the literature, clinical observations, and evaluation of the epidemiological data (such as age, occupation, habits, social history, etc.) were as scientific and precise as any well-trained physician could achieve today, lacking only the medical information and diagnostic tools that have appeared since his time. In other words, he is the paradigm of a brilliant biomedical scholar born too early to fully exploit his research.

My interest in this disease was stimulated by its unknown etiology, family acquaintances suffering from it, and a few potential epidemiological features that will be discussed below. It is a degenerative disorder of the central nervous system, stemming from the death of dopamine- generating cells in the substantia nigra region of the midbrain. The obvious clinically relevant symptoms appearing early in its course are motor in origin: shaking, rigidity, slowness of movement, and difficulties in walking and gait. Subsequent associations may involve dementia, depression, and emotional and sleep problems, which may ultimately prove to be more closely associated with aging than with a parkinsonian element. A small proportion of patients have first-degree relatives with the disorder, and several specific genes (SNCA and LRRK2), which code for alpha-synuclein, are closely associated with it.

The role of the SNCA gene may be important because the alpha-synuclein protein is the principal component of Lewy

bodies, a key pathological feature of the disease. Mutations in the LRRK2 gene, which encodes for the protein dardarin, also seem closely related to the disease when it is associated with a familial history.

As noted above, the principal pathological characteristic of Parkinson's disease is cell death in the substantia nigra. The proportionate neuronal loss at any time can be inferred by a neurosurgeon or necroscopist by estimating the reduction in melanin pigmentation of the substantia nigra in its pars compacta region. The remaining viable nerve cells still have Lewy bodies, and demonstrate the death of astrocytes and the activation of microglia.

A current conceptual model of the motor symptomatology of Parkinson's disease holds that the basal ganglia normally exert a constant inhibitory influence on a wide range of motor systems that prevents them from becoming active at inappropriate times. When a normal individual decides to perform a particular action, inhibition is reduced for the requisite motor system, thereby releasing it for activation. Dopamine acts to facilitate the release of this inhibition so that high levels of dopamine promote motor activity, while lower levels—such as occurs in Parkinson's disease—require greater exertions of effort for any given movement. Conversely, drugs that are used to treat this condition produce excessive dopamine activity, allowing motor systems to be activated at inappropriate times, thereby causing dyskinesias.

The diagnosis of Parkinson's disease is presently based solely on medical history and neurological examination. No laboratory tests are pathognomonic, and brain scans often function to simply rule out other diseases, such as Alzheimer's, cerebral infarction, and drug-induced Parkinsonism, rather than

to diagnose parkinsonism. Relief of motor impairments in patients treated with levodopa may sometimes confirm the diagnosis. Autopsy findings of Lewy bodies in the midbrain are often considered proof, and the progress of the illness over time may also help in confirming a diagnosis.

Efforts have been made to create useable diagnostic criteria for Parkinson's disease, though none are fully accepted as yet. The Parkinson's Disease Society Brain Bank suggests the following:

a) Bradykinesia (slowness of movement).
b) One or more of the following: rigidity, resting tremor, and postural instability.
c) Three or more of the following: unilateral onset, tremor at rest, progression over time, asymmetry of motor symptoms, 5+ year response to levodopa, clinical course of 10+ years, and dyskinesias induced by excessive levodopa.
d) Other possible causes for the above symptoms must be ruled out.

It is evident that criteria such as those noted above cannot be used as the basis for epidemiologically valid studies on the etiology of Parkinson's disease. When the definition of a disease to be investigated includes patients with and without diagnostic conditions that may be causally related, when arbitrary time spans are set for levodopa responses and for minimum periods of observation, and when other possibly related diseases may or may not be ruled out, the investigator finds himself beyond the possibility of studying a universe of patients with the same disease, which is a basic criterion of proper study design.

Nevertheless, in view of the substantial incidence of Parkinson's disease worldwide, its degenerative effects on the central nervous system, frequent confusion with cerebral arteriosclerosis and Alzheimer's disease, and elevated status as a cause of death among the elderly, it is worth studying even though strict adherence to classical epidemiological methods may be impossible. In creating an effective study design despite the absence of strict diagnostic criteria, the epidemiologist should begin by reviewing the major elements of the disease and its potential epidemiological consequences. After reviewing the clinical data, as outlined above, the epidemiologist must consider all confirmed or suspected aspects of the disease, including its possible causes, clinical associations, and other aspects of potential interest, before undertaking the design of a valid epidemiologic investigation.

This disease has been studied, systematically and otherwise, for some 200 years, although many essential issues remain unanswered. It has a number of generally accepted clinical stigmata, some of which may be incidental rather than causal. Diagnosis at an early developmental stage often lacks the typical neurological signs, and the midbrain cytopathologies, including Lewy bodies, may not yet be visible. Elderly patients with sequelae of cerebral arteriosclerosis and degenerative neuropathy may be mistaken for parkinsonians. Familial or senile tremors are often erroneously attributed to Parkinson's disease, even in the absence of rigidity and hypokinesia. A number of other relatively rare conditions in young patients (Wilson's disease, atypical Huntington's chorea, and progressive pallidal atrophy) as welI as in older patients (progressive supranuclear palsy, spastic pseudosclerosis, etc.) must also be ruled out. In addition, when selecting patients for epidemiologic study, it should be borne in mind that the disease is seen, diagnosed, and managed by a rather

wide variety of physicians with a diversity of basic knowledge about it, ranging from neurologists and neurosurgeons to internists, psychiatrists, and general practitioners.

There is agreement among most clinicians that the risk of Parkinson's disease increases with age, especially after 40, and predominates in males. There is also a clinical opinion, held by some, that the disease is less common among Afro-Americans than whites but this has not been supported by published studies until our own. Information concerning the genetics of the disease is now being generated, but there is little evidence yet of a substantial genetic relationship. A possible viral etiology has been proposed over the years, but most investigators agree that the Parkinson-like neurological symptomatology of the encephalitic viruses (Japanese B., St. Louis eastern and western equine, etc.) appear only in the acute phases of these infections, disappear thereafter, and are unrelated to the pathogenesis of Parkinson's disease.

Among patients coming to necropsy, a rather obvious pathological change is the grossly visible loss of melanin pigmentation in the substantia nigra. The major physiological lesion in vivo involves destruction of the nigrostriatal dopaminergic neuronal system, with a consequent reduction in dopamine levels of the basal ganglia region. The clinical stigmata of the disease can be substantially alleviated by administration of the metabolic precursor, L-DOPA, and dopamine itself cannot cross the blood–brain barrier.

In addition to the clinical findings and basic science correlations, we were interested in designing a study that would consider the well-known actions of nicotine on the central nervous system, especially the neuropathological effects such as tremors. Evidence that release of dopamine

and serotonin from the brain and other organs may be affected by nicotine was beginning to enter the scientific literature at the time of our study. These observations, together with those in three large prospective studies of mortality according to smoking habit, stimulated our interest in the possibility of an etiological relationship between nicotine and Parkinson's disease. Among 300,000 US military veterans, the risk of death from Parkinsonism was significantly lower in smokers and ex-smokers than in nonsmokers. Similar findings were obtained in studies of one million American Cancer Society volunteers and 41,000 British physicians, but these observations were not widely publicized (Kessler 1973, 88-105; Kessler 1978a, 355-385; Kessler and Diamond 1971, 16-25).

The findings in these three large studies, which were **not** designed to pinpoint risk factors in Parkinson's disease, and were not reported in the medical news of the time, greatly impressed me as a clinical epidemiologist. They reinforced our decision to undertake a study of Parkinson's disease, with special reference to its possible relationships to smoking and melanin.

DESIGN

After an intensive review of the clinical and basic science features of Parkinson's disease, a preliminary plan for a classical epidemiological study was drafted, based on the following two assumptions:

1. **Since there is as yet no agreed definition of Parkinson's disease, arbitrary criteria for the disease will not be used in the study.** During the planning phase of this effort, I traveled to the largest Parkinson's

disease center in the United States to speak with its medical director. His opinion was that since no agreed-upon diagnostic criteria for the disease exist, one must rely on the expertise of the doctors whose patients will participate in the investigation—a clearly imprecise and highly variable standard.

2. **The study will be based on a random sampling, over a three-year time period, of all patients diagnosed as having Parkinson's disease before or during their hospitalization in any Baltimore-area hospital by any licensed physician in the area.** Each case will be matched with the next patient hospitalized who is of the same race, sex, hospital, and year of hospitalization, and who was identified after a random start in the patient roster. The hospital charts of all the patients will be reviewed by physicians in order to validate the diagnosis of Parkinson's disease in the cases and confirm its absence in the controls. All information concerning neurologic diagnoses of any kind in the cases and controls will be abstracted (Kessler 1972a, 308-318).

Extensive personal interviews of the patients were conducted by trained personnel, who were not informed as to the case or control status of the respondents. A total of 525 parkinsonian cases were identified, of whom 468 (89%) were available for interview. Of the remainder, 7.4% declined to participate and 3.4% could not be located after their hospital discharge. During the several months of fieldwork, 54 (11.5 %) patients were deemed too ill for interview and 186 others (39.7 %) died before the scheduled interview. For all of the latter patients, interviews were conducted with next of kin. Analyses specific to patients diagnosed by neurologists and neurosurgeons versus those seen by all other clinical

specialists were also undertaken, whenever the numbers of patients in the desired categories were large enough to permit statistical analysis.

Fewer than 20% of the cases were hospitalized specifically for Parkinson's disease, suggesting that the cases were representative of parkinsonians in general rather than of clinically advanced cases in particular. The mean annual prevalence of Parkinson's disease during the three-year period of study among black Baltimore residents was consistently lower than among white Baltimoreans in each age and sex category, and significantly so for most. The risk of hospitalization with parkinsonism for blacks was one tenth that in whites below age 45, one quarter that in whites 45 to 64 years of age, and one quarter that in whites 65 and over. Not a single black male under age 55 was hospitalized with Parkinson's disease over the three-year study period, while 11% of the white male cases were in this age category. Among females, the corresponding differences were much smaller (Kessler 1972a, 308-318).

With regard to the usual findings in the literature expected for parkinsonian cases, the patients were very similar, except that a history of four common childhood exanthematous viral diseases were reported less often among them than in the controls. The relative risks for chicken pox, measles, German measles, and mumps were much reduced among them.

Among the conclusions in the case–control study, after reviewing previously published relationships between melanin, DOPA (dihydroxyphenylalanine), and other biogenic amines, was my suggestion of a possible etiologic pathway between these amines and nicotine. Also intriguing was the possibility that the apparent reduction in Parkinsonism among black

patients might be related to their increased body melanin pigmentation. A related question concerned the susceptibility of albino patients, who lack this pigment, to Parkinson's disease. A future study of black parkinsonians and controls of blood group antigens with known racial distributions might be one way to approach this problem. The question of whether common childhood exanthems in fact occur less frequently among parkinsonians also remains to be answered.

A public health consequence of this case–control study is that, in the years following publication of our results, a number of hospitals initiated trials of treating parkinsonian patients with nicotine administered in a number of ways, with varying—including a number of positive—results. While our findings led to active interest in further investigations on the roles of melanin and nicotine in the pathogenesis of Parkinson's disease, I was disappointed that such a promising clue to an important disease fostered by epidemiologic research was not pursued with the same vigor as, for example, the far more hazardous neurosurgical approaches to treatment. Clearly, active and ongoing dialogue between clinicians and biomedically knowledgeable epidemiologists might have led to more positive and clinically useful outcomes.

Hospital-based epidemiologic studies are often considered methodologically suspect by investigators concerned with the possible effects of differential hospitalization rates upon observed associations. This helps to explain the appeal of community-based studies in which patients are sampled from a population at large rather than from those hospitalized, the assumption being that such studies are less subject to selection biases. For this reason, among others, we then undertook a community-based epidemiologic study of Parkinson's disease in Baltimore, which was based on a general, rather than a

hospital-based, population. The investigation incorporated another feature, viz. a comparison of the characteristics of patients diagnosed by neurologists or neurosurgeons with those diagnosed by other physicians not specially trained in Parkinson's disease.

To initiate the community-based study, we obtained a computer listing of all private practitioners of medicine in Baltimore. The names of physicians with medical specialties unlikely to diagnose or treat parkinsonism (anesthesiology, gynecology, obstetrics, ophthalmology, pathology, pediatrics, and psychiatry, except for neuropsychiatry) were removed. The remaining names were randomized and stratified into five groups according to type of practice, viz. neurology and neurosurgery, general practice, internal medicine, general surgery, and all other specialties combined. A stratified random sample of 114, or 6%, of these physicians was obtained by selecting a predetermined number from each stratum. All members of the "Physicians' Panel for the Study of Parkinson's disease" sample were personally approached, and asked to identify and enroll in the study all of their Parkinson's disease patients who were seen over a recent three-year period (Kessler 1972b, 242-254).

In the analysis, the Physician's Panel was divided into two subpanels: a Neurological Panel consisting of all but two neurologists and neurosurgeons in Baltimore, and a Non-Neurological Panel comprising a stratified sample of other practicing physicians in the city. The physicians were requested to select as a control the next patient seen after a parkinsonian case who was of the same race, sex, and age but without Parkinson's disease. Trained personnel, who were not informed of the case or control status of each patient, then interviewed all patients at home. In addition, every fifth

interview was validated by a supervising interviewer who telephoned the patient, confirmed that the interview had occurred, ascertained the interview's date and duration, repeated the questions on smoking history, repeated the questions on encephalitis, and inquired whether any problems had arisen during the original interview. Case–control comparisons were analyzed by chi square, t-test, and z-test, and confidence intervals and relative risks were calculated as appropriate.

FINDINGS

The findings in the community-based study closely resembled those in the hospital-based case–control study (Kessler 1972b, 242-254). In particular, the lower Parkinson's disease prevalence among blacks was confirmed, as were the inverse relationships with smoking. The fact that both the community-based study and the case–control study yielded the same finding of lower Parkinson's disease prevalence among the black patients lends credence to this result in the real world, as may also be true for the observed inverse relationship with smoking. These results open the door to a variety of genetic causal possibilities that challenge today's overemphasis on the generic effects of poverty, malnutrition, and related social and environmental conditions on the nation's non-white population's illnesses.

Our findings in this large population-based study that black patients may be at a lower risk of parkinsonism than the general population was, we believe, the first to show a possibly biological, rather than an inadequate medical care, linkage to etiology. The medical literature is replete with articles on the cultural and educational differences that prevent blacks from seeking medical care, on the lesser

clinical training of primary care physicians treating black patients, on the less rigorous clinical facilities treating blacks, and on a multiplicity of other predictable and dead-end characteristics. While such characteristics may certainly affect the findings in clinical studies, the laxity with which they are defined for study and the broad acceptance of the view that blacks universally receive second-rate healthcare are so prevalent that it is often difficult to accept the findings of studies showing lower risks of disease among blacks. Parkinson's disease may be one such instance in which biology overcomes broad, but unsubstantiated, public opinion about inferior medical care in the black population.

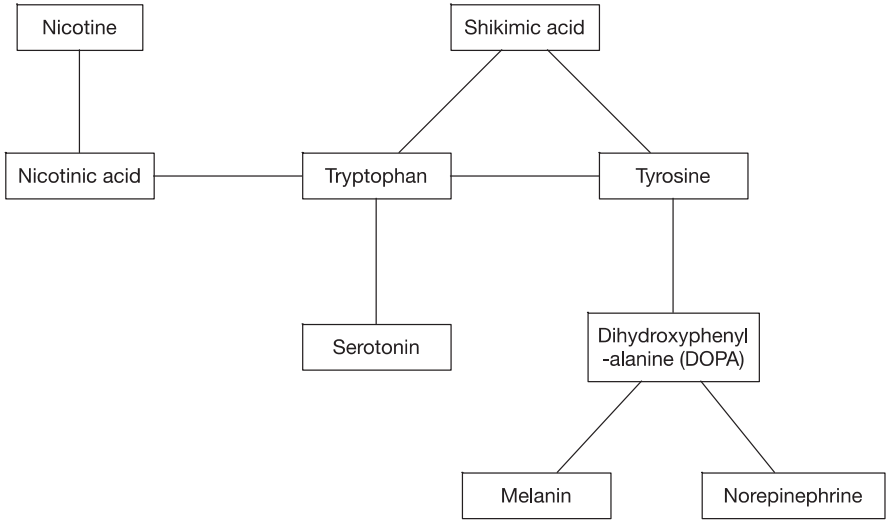
If a biological phenomenon is responsible for the lower Parkinson's disease rate in blacks, the responsible factor may be genetically transmitted, or related to patient environmental exposures and practices. Our study, which found a lowered risk in blacks, also revealed a decline in disease with tobacco use. Tobacco, particularly its nicotine component, has definite relationships to the central nervous system, and black individuals are more heavily endowed with melanin in and around the basal ganglia, as indicated by the locus, substantia nigra. We sought in our analysis to subject these factors to study in order to test whether blackness, or melanin and nicotine ingestion in tandem, might be related to our epidemiological findings and to possible new treatments for Parkinson's disease. Our hypotheses in regard to a diminished disease risk among blacks and among smokers were both confirmed, and, since these were posited long before the studies began, the results offer basic scientists and the clinical communities a pathway for further research on parkinsonian etiology and therapy.

DISCUSSION

As might be the case for other diseases as well, the reduced risk of Parkinsonism in blacks could theoretically be attributed to their increased melanin pigmentation. The known metabolic relationships between melanin, DOPA, and the other catecholamines shown in the figure below suggest a possible biochemical basis for the differential risk among the races. As noted above, information of relevance could be obtained from studies on the susceptibility of albinos, who lack melanin, to Parkinson's disease. Measurements in black parkinsonians and controls of blood group antigens with known racial distributions could serve as another approach to the general problem (Kessler and Diamond 1971, 16-25).

Nicotine has been employed in the treatment of post-encephalitic Parkinsonism, as well as being suspected of pathological involvement in Parkinson's disease for more than a century. Nicotine and parkinsonism also share relationships with dopamine, serotonin, and other biogenic amines. While the latter are deficient in the substantia nigra and basal ganglia of parkinsonians, their release from brain and other tissues may be affected by nicotine. In preparing our study in 1970, we summarized the then-known metabolic pathways of the biogenic amines as understood by clinical epidemiologists of the time. To the pathways, we added our view of where nicotine might fit into the general metabolic scheme.

Metabolic pathways of the biogenic amines



(Kessler 1972a, 308-318)

A number of years after our Parkinson's disease studies were published, clinical trials with nicotine patches and other modalities were undertaken, and substantial advances in basic science have accumulated in the intervening decades. In February 2014, the Michael J. Fox Foundation announced that it had raised $1.1 million for an international clinical trial on the potential of a nicotine skin patch to modify the progression of Parkinson's disease. Perhaps the slowness in follow-up is due to the reluctance of clinicians to accept epidemiological discoveries in imperfect human studies over their traditional acceptance of no less flawed laboratory-based studies on animals, tissue culture, and gene assays.

The observations that parkinsonians smoke less than other hospitalized patients, that relatively more of them stop smoking because of their disease, and that fewer of them have ever smoked support the possibility that nicotine may play a

role in the pathogenesis or clinical course of Parkinson's disease. So, too, does the small but consistent deficit of neurologic symptoms among male parkinsonians who smoke, as compared with those who do not. The tendency of smokers to develop their neurological symptoms at an earlier age than nonsmokers may be an artifact, but this might also argue for the existence of another form of Parkinson's disease, one which is more refractory to the effects of nicotine.

In another study of hospitalized veterans, it was observed that the parkinsonians did not smoke less but, rather, that the control patients smoked more than expected. But, in this study, the controls were selected from an unrelated investigation assembled a decade or more previously. To properly evaluate our own investigation, we compared the smoking habits of the control patients with those of a Baltimore population sample interviewed at about the same time. Although a somewhat different age classification had to be employed, the results showed that the two groups resembled each other rather closely in age, and, for both males and females, the control groups smoked slightly less than the population sample of similar age and race composition. We concluded that the differences in smoking habits between the parkinsonians and the general population in our hospital-based study were even greater than those observed.

Competing risks comprise another artifact, which could theoretically result in a spurious deficiency of smoking among cases as compared with controls. This might occur if patients hospitalized for conditions associated with smoking were less likely to have Parkinson's disease diagnosed, if present. While such a bias may, of course, occur in any study, it does not appear likely that the present findings can be explained on the basis of competing risks.

Nicotinic acid is a recognized end product of tryptophan metabolism. While structurally similar, nicotine has not been shown to degrade to nicotinic acid in humans. However, this possibility cannot be ruled out in view of the evidence that certain pseudomonas strains, as well as microorganisms derived from the surface of tobacco seeds, metabolize nicotine with the production of nicotinic acid. If this proves to be the case in humans, one would have a mechanism to define the role of nicotine in terms of its effects on the metabolic equilibria between tryptophan and tyrosine and the biogenic amines converted therefrom. Thus, it might be speculated that nicotine ingested via smoking is degraded in individuals constitutionally disposed to nicotinic acid. The latter might displace the equilibrium between tryptophan and tyrosine so as to increase the elaboration of DOPA. This, in turn, would prevent or decrease the risk of developing Parkinson's disease. The fact that parkinsonians who smoke tend to develop neurologic symptoms at earlier ages than nonsmokers might be explained on the basis of a different form of Parkinson's disease; one which is refractory to the effects of nicotine. This would, presumably, reflect genetic differences in biogenic amine metabolism between the two types of patients (Kessler 1972a, 308-318).

Another distinction between biomedical research in the post-World War II period and the present can be seen in the final paragraph of the paper described above. The investigators of that era, perhaps encouraged by growing federal government research support, were far more likely to objectively criticize their own work and that of their colleagues than would be the case today. Like the rest of society, the scientific community now often acts as if advancing scientific knowledge and separating truth from opinion should remain secondary to

avoiding conflicts with fellow scientists about important issues in the scientific world (Kessler 1978a, 355-385).

We also called for additional laboratory-based investigations of the known metabolic pathways of the biogenic amines to help account for the possibility that nicotine plays an etiologic or therapeutic role in Parkinson's disease, as well as the need for more epidemiologic studies in humans: "It is unlikely that the observed differences in smoking habits between parkinsonians and controls are due entirely to selection biases or other artifacts. If the differences are real, they require an explanation. The known metabolic pathways of the biogenic amines are suggestive of a possible mechanism, under the assumption that nicotine can be degraded to nicotinic acid in man, as it is in certain bacterial strains. Clinical and laboratory investigations of this hypothesis would be in order. These might include prospective studies on the long-term neurologic effects of smoking, as well as controlled observations on the metabolism of nicotine in persons with and without Parkinson's disease." (Kessler and Diamond 1971, 16-25).

Chapter Five Summary

Tonsils and Adenoids: Do They Play a Role in Human Cancer?

Numerous investigators have considered possible functions of the tonsils, adenoids, and appendix in infection and immunity for many years, but conclusive epidemiological studies in this arena are rare. It is said that the basic function of these organs is to become infected in order to supply antigens for maintaining the tonus of the immunological system. The bodily locations and other similarities to rabbit appendix and chicken bursa fabricii suggest that the appendix may function as a central lymphoid organ, secondary in importance only to the thymus.

For the clinical epidemiologist, definitive studies on the possible role of these lymphoid tissues in neoplasia might follow the design of a study that we undertook some years ago. This was a prospective study (conducted in retrospect) of patients undergoing lymphoid surgery (tonsillectomy, adenoidectomy, or appendectomy) at the Johns Hopkins Hospital, who would be compared with a control group having non-lymphoid surgery at the hospital at the same time.

The advantages of this design include the following:

1. The prospective approach would reduce the bias of retrospective designs.

2. The follow-up averaging 45 years encompasses the major decades of cancer risk.
3. The large cohort size would permit the study of multiple outcomes.
4. The large sample of children would allow study of cancer risk by age at surgery.

The study was highly favored by our Department of Preventive Medicine as an investigation worth undertaking at the time. It remains a promising project for epidemiology, since there is still much to be learned about the role of lymphoid organs, and despite the current slowdown in such public health investigations.

CHAPTER FIVE

TONSILS AND ADENOIDS: DO THEY PLAY A ROLE IN HUMAN CANCER?

BACKGROUND

Immunologic abnormalities are associated with a number of neoplasms in humans, most impressively in Hodgkin's disease, multiple myeloma, and chronic lymphatic leukemia. A significant proportion of such patients develop hypogammaglobulinemia, with monoclonal malignant expansion of the B-cell population. The susceptibility of Hodgkin's disease patients to mycobacterial, herpetic, and other infections has been attributed to an early and progressive cellular immunodeficiency. Other possible aberrancies of immune mechanisms may be operative in cancers of the breast and colon, inter alia. The extent to which immune responses of the human cancer host are primary, and therefore implicated in the carcinogenic process, or merely secondary effects of interaction with factors like viral agents, is being studied in many laboratories.

Whatever pathophysiology is ultimately confirmed, it seems clear that successful malignant adaptation (i.e. neoplastic transformation) involves an effective abrogation of the host's immunologic resistance at some point in the carcinogenic process. The more effective the host's immune defenses, the more delayed the onset of tumorigenesis, the greater the carcinogenic "dose" required, or the slower the clinical course

and the longer the host's survival. Ineffective host defense mechanisms should be associated with early tumor susceptibility, fulminant clinical course, and diminished survivorship.

At present, there is general agreement on the central roles played by the mammalian thymus and the avian bursa of Fabricius in the immune response, particularly in early life. The relationship of the thymus to oncogenesis is also under active scrutiny. However, the role of other lymphoid tissues in neoplasia has been much less intensively explored.

Possible functions of the palatine tonsils in infection and immunity have been considered for nearly a century. In recent years, some physiological activities of this organ and the adenoids have been proposed, and observations made on their antibody production. An argument favoring such activity has been succinctly put:

> The exposed position of tonsils and adenoids in the pharynx, and their frequent involvement in viral infections, lead to the surmise that these tissues have the function to be infected and serve the body by supplying antigens on a physiological level in health, and thus maintain the tonus of the immunological system. Tonus of the immunological system means readiness of the lymphatic tissues to react to antigens, with the production of antibodies.

Ogra (1971,59-64) has reported that tonsillectomied children produce less nasopharyngeal IgA anti-polio antibody upon administration of attenuated oral poliovirus than do untonsillectomied children. He suggests that this is due to extirpation of secretory IgA-producing tissue, i.e. the tonsils. Alternative explanations relating tonsillectomy and antibody deficiencies to an underlying immunodeficiency state have been offered by others, but it is now known that the palatine tonsils contain both B- and T-cells with immunologic

competence, and that germinal center development occurs following antigenic stimulation at these sites.

The vermiform appendix has also aroused the interest of immunologists and oncologists in recent years, primarily as a possible mammalian analogue of the avian bursa of Fabricius. In studies on the ontogeny of mammalian lymphoid tissues, Cooper, Gabrielsen, and Good (1967, 113-138) demonstrated that, while the thymus develops first, the appendix also evolves normally in neonatally thymectomized rabbits. Furthermore, striking similarities are noted in the histologic appearance of rabbit appendix and bursa fabricii of chickens, during their development and at maturity. These findings suggest that the appendix may function as a central lymphoid organ, albeit secondary in importance to the thymus under normal circumstances.

The laboratory findings on the possible roles of these lymphoid organs in immunity and carcinogenesis in the mid-1960s led to a series of clinical or epidemiologic tests of the underlying hypothesis. Utilizing a series of 914 autopsies from three institutions in Kansas City, McVay (1964, 929-937) noted a significantly increased incidence of prior appendectomy in colon cancer patients compared to controls with vascular disease. Similar findings were obtained for persons dying from a variety of other cancers, especially below 60 years of age, but several other studies failed to show such relationships.

After reviewing the literature that pointed in no specific direction, we drew the following conclusion: Two promising approaches are open to epidemiological investigators on the possible role of lymphoid entities in neoplasia. First, one might design **a well-controlled retrospective study of**

appendectomy and tonsillectomy status in persons with and without cancers of specific types. Such a study should have sufficient numbers of cases and controls to assure an adequate test of the hypothesis. It should also provide for an independent validation of reported appendectomy or tonsillectomy status, perhaps through a review of all existing hospital records. A second approach would be the **prospective follow-up of a suitably large cohort of persons appendectomied or tonsillectomied several decades earlier, and suitable controls.** The true risk of cancer in each group would then be calculated.

The retrospective studies mentioned above are characterized by substantial variability in findings, which probably stems from variations in methodological details. In many studies, appendectomy or tonsillectomy rates were not adjusted for age or sex differences between cases and controls. Controls, in turn, were often selected from among patients hospitalized during different time periods than the cases. Response rates in interview studies were often low and variable in patients with and without cancer. Mailed questionnaires were sometimes employed, which precluded the possibility of validating patient responses on lymphoid organ surgery.

To our knowledge, only one prospective study of the lymphoid tissue/neoplasia hypothesis has been conducted to date. This was the relatively small, but elegantly designed, investigation of McVay (1967, 439) who identified 626 appendectomied patients and 583 other patients, and then matched their names against those in the Connecticut Tumor Registry. A large excess of subsequent deaths from neoplasms of the colon, lung, breast, stomach, and esophagus was noted among those appendectomied. However, any causal inferences must remain tenuous because: (a) no primary appendectomies

were included; (b) most appendectomies were performed after age 40; (c) sample sizes were insufficient for the analysis of any specific tumor; and (d) there were systematic shortcomings in the Connecticut Tumor Registry itself.

DESIGN AND ANALYSIS

We decided to investigate the possible immunologic functions of three lymphoid organs in human cancer, utilizing the existing records of the Johns Hopkins Hospital. The proposal was to design a prospective study, conducted in retrospect, in order to reduce the confounding seen in previous studies (Kessler 1970c, 510-522*).* The following were the principle design elements of the study:

1. The **prospective approach would eliminate selective biases** inherent, to some extent, in case–control approaches;
2. **Large cohorts** of tonsillectomied, adenoidectomied, and appendectomied patients and controls **would be included**;
3. **Follow-up would be for an average of 45 years**, i.e. exceeding the expected life-spans of many of the patients and encompassing the major decades of cancer risk for most propositi;
4. **Sufficiently large samples of children would be included**, so as to permit inferences on the influence of age at surgery on eventual cancer risk;
5. **All possible outcomes (survival/death with or without any type of cancer and other diseases) would be studied**. This feature differentiates the study from the small number of specific outcomes that can be investigated in most retrospective studies.

The study would have seven specific aims:

1. **To identify "case cohorts" of patients without a previous history of cancer who underwent tonsillectomy, adenoidectomy, and/or appendectomy for reasons unrelated to cancer**, at the Johns Hopkins Hospital between 1925 and 1936.
2. **To identify "control cohorts" similar to the case cohorts in age, sex, and race, and without a previous history of cancer, who underwent surgery other than tonsillectomy, adenoidectomy, or appendectomy for reasons unrelated to cancer**, at the Johns Hopkins Hospital between 1925 and 1936.
3. **To trace the patients of each cohort from the time of their lymphoid tissue or control surgery to death or survival** as of December 31, 1974, viz. the end of the observation period.
4. **To ascertain the causes of death of all cohort decedents**, utilizing death certificates and, possibly, hospital pathology records.
5. **To explore the possibility of ascertaining total incident cancer cases** in all, or a sample of, the cohort patients through the end of the observation period.
6. **To compare the risk of subsequent cancers**, total and site-specific, in the various case and control cohorts and at varying intervals of time following surgery.
7. **To make inferences concerning the roles of the palatine tonsils, the adenoids, and the vermiform appendix in human cancer risk**.

We felt that this study would benefit from the fact that the Johns Hopkins Hospital had a well-organized and accessible information system on all inpatients seen from 1925 to the present. Unfortunately, the study was completed and analyzed

but not funded. There were difficulties arranging for a faculty member to lead the study, and departmental funds at the time were inadequate for patient follow-up. There was no opportunity to prepare a formal grant application, and shepherd it through the university and funding agency bureaucracies. The overwhelming interest of the present generation's bioscientists in genome assays and Big Data research would probably make them even less likely to undertake such a classical epidemiologic study than a generation ago.

THE PRESENT

CHAPTER SIX SUMMARY

BLADDER CANCER AND THE ARTIFICIAL SWEETENERS

Saccharin, an artificial sweetener discovered in 1879, became widely popular after cyclamate, a hexylsulfamate sweetener synthesized in 1937, was combined with it to yield a stable, sugar-like substitute without a bitter aftertaste. By 1960, artificially sweetened diet drinks were accounting for 15% of the soft drink market, a proportion that has risen dramatically since then.

To counter this major threat, Abbott Laboratories sponsored a university-based study on the effect of feeding cyclamates to rats, a few of which developed bladder tumors. The result quickly led to the banning of cyclamate, even though officials of the Department of Health, Education, and Welfare (HEW), and the Food and Drug Administration (FDA) disclosed that none of the test rats had been fed pure cyclamate, and thus cast doubt on their conclusions.

The government's ban was of concern because of its alacrity, sparseness of evidence, and apparent lack of objective concern for food and drug safety. Furthermore, one of my earlier studies failed to demonstrate that urinary tract cancer was increased among diabetics who used non-nutritive sweeteners (NNS). This led us to submit a federal proposal for an epidemiological investigation of Baltimore-area residents with bladder cancer who were discharged from 19 hospitals

between 1972 and 1975. Control subjects were randomly selected from each hospital's roster of cancer-free patients without bladder conditions, who were hospitalized at the same time, and were of similar sex, race, age, and marital status to the cancer patients.

The patients and controls were subjected to an intensive personal interview focused on smoking habit, lifetime occupations, and NNS intake. The use of NNS was assessed in terms of relative risk and dose–response relationships. No evidence of any hazardous effects of NNS was demonstrated.

Ours was the first of a handful of studies on this important public health issue, and, since then, no evidence of carcinogenicity has emerged. Yet, the FDA's original decision on NNS carcinogenicity has not been modified.

CHAPTER SIX

BLADDER CANCER AND THE ARTIFICIAL SWEETENERS

BACKGROUND

Saccharin, an artificial sweetener discovered in 1879, has been the subject of a wide variety of studies. The literature of the late Victorian era is replete with conflicting reports on its value in diabetes mellitus, as well as for treating various gastrointestinal and other conditions. In 1912, a Board of Scientific Advisers to the Secretary of Agriculture appointed by President Theodore Roosevelt concluded that 0.3 grams per day of saccharin was safe, but an intake exceeding 1.0 gram per day causes digestive disturbances.

During World Wars I and II, saccharin consumption greatly increased in Europe without any apparent adverse effects, although no epidemiological studies of the consuming public were undertaken. Between the wars, findings in numerous toxicological studies on experimental animals raised no serious questions about the sweetener's safety. A National Academy of Sciences (NAS) committee reviewed the existing data in 1970, shortly after the banning of cyclamate in 1969, and concluded that saccharin was safe, but it suggested further toxicologic investigations as well as comparative studies on the relevant metabolic processes in both animals and human subjects.

In 1954, as saccharin became more widely used in the American diet, the NAS Committee on Food Protection reviewed the toxicological literature on the subject and concluded that the maximum tolerance level for saccharin in the human diet was at least as high as 1.0 gram per day. Another report by the NAS Committee on Food Protection in 1968 came to a similar conclusion, but recommended that new studies be undertaken, utilizing higher levels of testing than those in current use.

Cyclamate, a hexylsulfamate sweetener usually combined with smaller amounts of saccharin for human use, was synthesized by Dr. Michael Sveda, a doctoral student in chemistry at the University of Illinois in 1937. It was patented by DuPont, licensed to Abbott Laboratories, and marketed with saccharin beginning in 1950, to sweeten soft drinks and canned foods. Saccharin had already been on the market for 60 years, but it possessed three negative characteristics that could be eliminated by adding cyclamate: its sweetness was far less sugar-like; it became bitter in concentrated solution; and it was unstable to hydrolysis even in the presence of acids. During the succeeding decade, cyclamate production increased by more than 300%, and diet drinks alone came to account for some 15% of the total soft drink market.

The major victim of this economic boom was the $2-billion sugar industry, whose executives became concerned about the adverse effects on their market and also about the psychological impact cyclamates were having on the consumer. This was a time of rising diet-consciousness in America, and there was an increasing tendency to point an accusing finger at sugar as being responsible for serious health hazards. Many sugar producers feared that if the cyclamate boom continued unchecked, the industry would

eventually lose a significant percentage of its annual sales to the NNS.

The sugar industry went into action. In 1966, Sugar Information Inc., its promotional arm, advertised on television for the first time, earmarking most of its budget for this purpose. Two years earlier, in 1964, the Sugar Research Foundation contracted with the Wisconsin Alumni Research Foundation to launch a study on the effects of feeding cyclamates to rats. This study was then expanded in both the United States and England in an effort to find other possible health hazards in cyclamates. These efforts paid off brilliantly when cyclamates were suddenly withdrawn from the US market in 1969. The details of this triumph of pseudo-science should be of interest to health professionals, the general public, and the government, and were of great interest to me as a clinical epidemiologist.

Abbott Laboratories, the leading cyclamate producer, was concerned about the etiological notices spread by the sugar interests and sought ways of dealing with consumer activist groups who were attacking chemical additives like cyclamate. Their solution was to hire Dr. Bernard Oser, a prominent biochemist and food industry consultant, to make further tests on the safety of cyclamates at the Food and Drug Research Laboratories of which he was the chairman. On October 8, 1969, Dr. Oser notified Abbott of the presence of tumors in several laboratory rats, which were reviewed by their pathologists and reported to scientists at HEW. A week later, officials of the FDA met with National Cancer Institute scientists, and, the following day, HEW Secretary Robert H. Finch announced that the government was removing cyclamate from the Generally Recognized as Safe (GRAS) list following the requirements of the Delaney Clause of the

Food Additives Amendment, because research indicated that cyclamates caused cancer in rats. This, in turn, led to increasing pressure from Congress, which finally banned cyclamates, even for limited medical use.

The economic impact of the cyclamate ban was immediate. Abbott took a $3.5-million write-off on its cyclamate business. The ban virtually dried up sales of its popular low-calorie fruit line. Calcan was left with heavy inventories of tinware, uncompensated in any way. The soft drink industry was hit equally hard, but the fanfare of publicity given the ban and the haste at which the FDA moved was very unusual. The ban had been announced 24 hours after the FDA/NCI meeting at a special news conference called by HEW Secretary Finch. And, literally within days, a number of other nations followed the US in banning cyclamate without even being informed of the evidence upon which the HEW decision was based.

Four months later, on February 20, 1970, an article appeared in *Science*, the official publication of the American Association for the Advancement of Science, signed by high-level officials of the HEW and FDA among others. It disclosed that the rats in the Abbott tests, which had been the major reason for the ban, had not been fed doses of pure cyclamate but, rather, a mixture of high doses of cyclamate, saccharin, and cyclohexylamine (a converter of cyclamates), and that papillary transitional cell tumors were found in the bladders of several rats. When a mixture of ingredients produces a certain effect, it obviously cannot be decided which agent, if any, is responsible without further rigorous testing. By the logic of the FDA in this case, saccharin could have been the cancer-causing agent, but, for still rather obscure reasons, cyclamates were singled out as the culprit. Several of the other studies cited by the FDA were not even

designed as cancer tests, and the results were neither dose-related nor conclusive.

In 1970, Professor Dietrich Schmahl, chairman of the Cancer Research Center in Heidelberg, conducted an independent study using many more rats than the American investigation, and extended the follow-up to cover the entire lifetimes of the animals, in contrast with the American study that sacrificed the rats two years after initiating the NNS diets. Although Schmahl used extremely high dosages of pure cyclamate—80 to 240 times greater than in traditional human consumption—he was unable to detect any evidence of carcinogenicity. Since the publication of the Schmahl and Habs paper (1980, 1905-1906), several dozen studies on animals and on humans have been conducted in the US and abroad, none of which have concluded that cyclamates were unsafe or carcinogenic.

The governmental ban on cyclamate in 1970 alerted my interest because of its sudden passage, sparseness of evidence, and seeming lack of systematic concern about food and drug safety, as well as the results of my earlier studies of cancer risk among diabetics which yielded no evidence that urinary tract cancer was increasing among diabetics, the likeliest subpopulation to regularly ingest artificial sweeteners. The fact that the government was relying heavily on animal studies, with little interest in human studies, was another cause of concern to me. While some toxins and carcinogens may affect different species similarly, there are many examples of a single species, or subspecies of animal or plant, being uniquely susceptible or resistant to a toxic agent, or to the dosage and duration of treatments chosen for study.

DESIGN

Having decided that studies of human population risks, as difficult as they sometimes are to mount, should be included to help resolve the artificial sweetener controversy precipitated by the government's action, I prepared an epidemiological study of the case–control variety. The investigation would begin with an extensive investigation of all artificial sweeteners sold or distributed by type in the Baltimore region since 1960. All Baltimore-area residents with bladder cancer, discharged from its 19 participating hospitals between1972 and 1975, were identified. The only other general hospital in the region, a small one, had no urologic service. Out of a total of 634 patients with histopathologically confirmed malignant neoplasms of the bladder, 519 (82%) agreed to participate in the study. Those excluded were senile, dying, otherwise unable to be interviewed, and refusers. Control subjects were chosen in random fashion from each hospital's registration list of cancer-free patients without bladder conditions who were hospitalized in the same hospital at approximately the same time as the bladder cancer patients, and who were of the same sex, race, age (+/- three years), and current marital status. In less than 7% of the cases did non-participation necessitate our selecting more than two controls for inclusion in the study (Kessler 1976a, 143-146; Kessler and Clark 1978, 349-355).

All patients and controls were subjected to an intensive personal interview with respect to smoking habits, occupational history, and intake of NNS. The latter was probed in terms of table sweeteners, diet beverages, diet foods, and total usage in all forms. For each specific NNS-containing substance, information was obtained on the frequency, quantity, and duration of use by type and brand name. To reduce the likelihood of including cancers unrelated

to sweeteners, ingestion of saccharin or cyclamate one year before the date of cancer diagnosis and thereafter was ignored for each patient and matched control. The interviewers were not informed of the case or control status of the subjects scheduled for interview.

Relative frequencies, quantities, and duration of NNS use among patients and controls were calculated, and the statistical significance of all differences was computed. Comparisons were also made in terms of relative risk, with and without simultaneous adjustment for potential confounding factors. In addition, the data were examined for evidence of dose–response relationships, which might shed some light on the nature of the association between NNS and human bladder cancer. Wherever possible, the effects of saccharin and cyclamate on bladder cancer risk were also examined separately NNS use was assessed in terms of relative risk and dose–response relationships.

FINDINGS

The proportion of patients and controls that had ever used NNS in any form was essentially the same. As to NNS powders, tablets, or drops, there were no substantial differences in mean servings per day, mean days per week, or mean years of use among the male subjects and controls. The female cases tended to use somewhat more NNS tablets, although over a shorter period of time than their controls. However, the mean years of NNS drops intake was significantly greater among the female controls ($P<0.01$).

Exposure to artificially sweetened beverages of all kinds was equivalent in patients and controls of each sex. With few exceptions, the same applied to NNS-containing diet foods.

Use of diet ice cream was reported more often by bladder cancer patients, but there were no significant quantitative differences in exposure. Diet pastry and salad dressings were eaten by the cases for significantly fewer years. In general, the relative risks of bladder cancer were not significantly increased by NNS use, whether matching of case–control pairs was taken into consideration or not. The only exception was diet ice cream, for which the relative risk among women alone was 3.50.

An overall relative risk of bladder cancer among NNS users, simultaneously adjusted for smoking habit, occupation, age, race, sex, diabetes mellitus, and several other potentially confounding factors, was calculated using a multiple regression method. The observed value of 1.04 was insignificantly different from the null value 1.00. Comparable figures specific for men and women were 1.11 and 0.80 respectively, also not significantly different from 1.00. To examine the relationship between bladder cancer and NNS dose, study subjects were divided into three equal groups according to the level of lifetime NNS exposure. Patients, both men and women, tended to report relatively more NNS use at low levels, but relatively less at medium and high levels, than controls.

Use of table sweeteners was somewhat exceptional in that cases exceeded the intake of controls, though insignificantly, in prevalence of high exposure levels. The only significant difference was among women drinking low levels of diet beverages ($P<0.05$). When these figures were adjusted for possible confounding factors and transformed into risk ratios, no evidence of an increase in relative risk with increasing exposure level was apparent.

Patients and controls did not differ significantly in the proportion that ate or drank foods containing either saccharin or cyclamate. The relative risks of bladder cancer among saccharin and cyclamate users were 1.01 and 0.97 respectively for both sexes combined. Male patients had somewhat higher, but still insignificant, odds ratios compared with female patients. On average, saccharin was consumed for significantly shorter periods by patients than by controls ($P<0.05$). The same was true for cyclamate. In mean serving-years, there were also no significant differences between patients and controls for either of these sweeteners.

Relative risks of bladder cancer by specific sweetener use did not significantly differ from 1.00 in either men or women. However, odds ratios tended to be somewhat higher than null value in men and somewhat lower in women. When relative risks of bladder cancer were calculated separately for smoking and nonsmoking NNS users, these were found to be 0.84 among smokers and 1.36 among nonsmokers, neither significantly different from 1.00. The highest relative risk (1.69) observed in male nonsmokers did not differ significantly from 1.00. However, when this figure was adjusted for possible confounding factors by a multiple logistic method, the calculated relative risk of 2.61 had a 95% confidence interval of 1.20 to 5.67.

Exposure histories of the patients to cigarettes and other tobacco products were specifically elicited. Patients were significantly more likely than controls to use tobacco and to smoke cigarettes ($P<0.01$). Men smoked for approximately five years longer on average than their controls ($P<0.01$). Relative risks for bladder cancer among smokers were 1.78 and 1.57 in men and women, respectively.

Patients were also more likely than controls to have graduated from high school and to be widowed or divorced. Diabetes mellitus was slightly less prevalent among them, and relatively fewer were of the Jewish faith. Otherwise, the bladder cancer patients were demographically similar to the controls, both in toto and by sex.

The relative risks for bladder cancer among NNS users, which were detectable at varying beta levels in this investigation, were estimated by the arcsine transformation method. A 37% increase in bladder cancer risk was detected among NNS users with a power of 80%, assuming that the population prevalences of NNS use approximated those of the control patients.

This study was conducted on subjects comprising a high proportion of the recently diagnosed bladder cancers in greater Baltimore who survived to the interview date. Of these, 93.4% experienced their cancer onset within four years of the study. Of the patients and their controls, 17% were treated at one hospital, 14 % at another, and decreasing proportions at each of the other 17 hospitals.

Accordingly, study subjects were probably representative of the community at large, rather than of any given institution. Their selectivity was further reduced by including most newly diagnosed cases and by matching them to demographically similar controls. The patients were interviewed blindly and intensively on NNS use in all forms. Brand names were recorded, and NNS constituents during the years of the study were verified from industrial sources and by direct examination of product labels. The exclusion of NNS use up to one year before cancer diagnosis in all patients and their

matching controls served to reduce the possibility of bias even further (Kessler 1979a, 996-998; Kessler 1980a, 583-593).

DISCUSSION

Our findings suggest that ingestion of NNS, at least at the moderate dietary levels reported by the patient sample, is not associated with an increased risk of bladder cancer. This conclusion is strengthened by the consistency of the normal findings for nearly all NNS-containing substances, with frequency, quantity, and duration of use considered. It is further substantiated by the persistence of the findings after simultaneous adjustment for the effects of smoking, occupation, age, diabetes mellitus, and several other potentially confounding factors. The failure of the relative risk of bladder cancer to increase with increasing NNS exposure is also inconsistent with an etiological relationship. However, cyclamates were introduced too recently to permit the detection of carcinogenic effects appearing more than 10 or 15 years after initial exposure.

Two apparently contradictory findings are in need of explanation. First, there was a tendency of relative risks in male, but not female, NNS users to exceed 1.00, though insignificantly so. Second, there was an increased relative risk in nonsmoking male, but not female, NNS users. The fact that the odds ratios in men exceeded those in women by a similar order of magnitude for total NNS use, as well as for saccharin alone and cyclamate alone, suggests the possibility of an artifact at work. Saccharin and cyclamate are chemically distinct, so that they would not be expected to produce the same effect. Furthermore, the men drank significantly more cups of coffee per day than their controls ($P<0.01$), while there were no differences among women. Coffee is often

sweetened with NNS and has been suggested as a bladder carcinogen. Thus, the sex difference could, at least in part, reflect differences in coffee habit rather than NNS exposure per se.

Since the insignificant relative risks were adjusted for smoking habit, the findings among male nonsmokers may also be artifactual. Male nonsmokers were significantly older and more likely to have memory problems at interview than their controls ($P<0.05$). Both of these phenomena need further study. In any event, the findings do not suggest an interaction between smoking and NNS that increases bladder cancer risk.

The Canadian study that precipitated the FDA action was not designed to evaluate the carcinogenicity of saccharin but rather to differentiate between the effects of saccharin and its major contaminant orthotoluenesulfonamide (OTS). Accordingly, only one level of saccharin was employed, which thus made it impossible to generate information on the presence of a dose-related response to the sweetener. In contrast with other carcinogenicity experiments, the animals were not sacrificed for necropsy at scheduled intervals during the trials; instead, they were simply examined each day for clinical signs of tumors. This apparent weakness in the study protocol may be responsible for the confusion that persisted with respect to the precise number of bladder tumors developing in different trial groups. At various times, it was suggested that 14, 12, or 8 of the second-generation male rats had developed histopathologically confirmed bladder cancer. But 12 out of 50 first-generation treated rats and 14 out of 50 control rats were unaccounted for, as were 5 out of 50 second-generation treated rats and 8 out of 50 control rats. Another cause of concern is that the second-generation tumors that developed among the Canadian study rats, and possibly

among those in the Wisconsin Alumni Research Foundation (WARF) and FDA studies as well, appeared to be unlike human bladder carcinomas in their low degree of invasiveness and complete absence of metastases.

Some discrepancies between our findings and those in the Canadian study may stem from subtle differences in the populations studied. Additionally, a few rather unique features of the Canadian study may have played a role. For example, the patients in the latter study were apparently queried on their use of tablet or drop sweeteners but not on powders. Their interviews also omitted the ascertainment of the calendar period during which sweeteners were used; thus, the analysis may have included subjects who used saccharin after the onset of their cancer. Other possible discrepancies were the apparent exclusion of all saccharin-containing substances whose brand names were not provided by the Canadian subjects or whose saccharin-content could not be determined. Finally, the Canadian study's analysis of saccharin use on an "ever or never" basis could be subject to bias if the patients and the controls differed in the proportions reporting single, one-time, or occasional use as opposed to substantial use.

Some anomalies in the FDA and WARF studies also require resolution. For example, in the FDA study, more bladder cancers occurred among the male control rats than those fed saccharin, except at the 7.5% dose level. In fact, rats fed moderate dosages of saccharin actually had a lower incidence of bladder hyperplasia than the controls. In the WARF study, very small numbers of animals were employed, and bladder tumors were found only among male rats at the highest saccharin dose levels. To increase the confusion, the incidence of adrenal, pancreatic, and other tumors was considerably higher among the control rats than among rats

exposed to saccharin. There is also some evidence that rats clear high doses of saccharin differently than they clear low doses, as the mechanism for renal tubular secretion becomes overloaded. This alone would make it difficult to justify extrapolation from high-dose to low-dose animal experiments, let alone to low-dose human exposures.

Around the time of these studies, a number of short-term in-vitro tests were developed for use in predicting whether substances are likely to cause cancer. Most commonly, these evaluated the extent to which suspect substances (such as saccharin) are mutagenic or interactive with DNA. The large majority of the short-term tests for genetic effects of saccharin and some of its impurities have been negative. Thus, the substance may not even be mutagenic, although more research on this question is necessary. The Committee for Study on Saccharin and Food Safety Policy of the National Academy of Sciences, appointed by the National Research Council, concluded from its deliberations that "either saccharin is unusual in that its carcinogenic effects are due to the unmetabolized parent compound or the effects are due to small quantities of undetected metabolites. The committee was led to this conclusion because little biotransformation of saccharin has been detected in laboratory animals and none at all has been observed in humans. The fact that people do not metabolize saccharin but excrete essentially all of it unchanged in the urine poses a formidable problem to those who support its carcinogenicity in humans.

Certain technical problems have added to the difficulties in interpreting the toxicologic studies. For example, the tumors observed in the in-utero studies were often associated with altered urine composition and crystalluria. In addition, these animals often demonstrated body weight losses in excess of

10%, suggesting that the experiments might have been conducted at saccharin levels exceeding the maximum tolerable dose. One might also ask whether it is appropriate to employ saccharin dosages that kill 50% of the rats due to toxicity long before the anticipated development of cancer among the survivors. The other effect of these high dosages—i.e. saturation of the renal tubular secretion mechanism—becomes manifest at approximately the 5% dietary level of saccharin. Therefore, at feeding dosages exceeding 5%, the excretion of other, possibly carcinogenic, metabolites may be impeded and thus produce bladder cancers that are fundamentally unrelated to the saccharin.

An important element in generalizing the results of ad hoc studies, whether laboratory-based or epidemiological, is the existence or nonexistence of biological consistency among the studies. In the present instance, for example, our findings appear to be more consistent in several respects than the Canadian study. The divergence in relative risk between the male and female Canadian cases attributable to NNS use would be extraordinary for most human carcinogens, and there is no evidence to support the metabolic differences suggested as an explanation by the authors. An equally puzzling, if not biologically inconsistent, finding was the Canadian authors' observation of an increased relative risk for users of saccharin tablets, but not for users of saccharin-containing drinks or foods (Kessler 1980b, 243-269).

An apparent absence of an association between total NNS use and bladder cancer suggests that neither saccharin nor cyclamate in physiologic dosages is carcinogenic in humans (Kessler 1980c, 1091-1110). One of the alternative explanations, viz. that one of these substances is carcinogenic while the other is protective against cancer, is unsupported by any

scientific evidence at this time. More importantly, it is contradicted by the saccharin-specific and cyclamate-specific data presented here.

Ours was the first of a handful of studies on this important public health issue, and, since then, no evidence of carcinogenicity has emerged (Kessler 1977c, 129-132). Yet, the FDA's original decision on NNS carcinogenicity has not been modified.

Chapter Seven Summary

Cervical Cancer, Intercourse, and HSV-2 Infection

Like Ramazzini, Rigoni-Stern of Padua was an early advocate of epidemiological reasoning in medicine. Utilizing municipal records, he analyzed cancer mortality in Verona between 1760 and 1839, and observed an inverse relationship between the two commonest cancers of women: breast cancer in unmarried women and religious sisters, and uterine cancer among the married and widowed. Over the past few decades, the case mix, by clinical stage, of cervical cancer has changed dramatically, with carcinoma in situ increasing in all classes of women. The explanation probably lies in substantial changes in diagnostic practices, the near universality of Pap testing, and exposure of increasing proportions of women to the presumptive etiological risk factors.

A joint investigation undertaken with my wife and colleague, Prof. Laure Aurelian, a highly experienced leader in virology and immunology, was designed to answer the following question: What is a woman's risk of developing cervical cancer if she is married to a man whose previous or subsequent wife had this disease? The study began with the identification of the probands: several thousand women with invasive or in situ cervical cancer diagnosed between 1950 and 1969 at the Johns Hopkins Hospital. Their husbands were identified, and all other wives of these husbands were followed prospectively for the development of cervical

cancer. For each “other wife,” a control woman similar in age, race, year of marriage, and prior marital status was randomly selected from marital records of the geographic area and similarly followed.

Patient follow-up ended when 1,889 “other-wife” probands and 1,626 matching control wives had been assembled and traced. The results suggested that women marrying men whose previous wives had cervical cancer incur a risk 2.5 times greater than normal for developing this disease. These findings add to the evidence that an important causal factor in cervical cancer is venereal in nature, and is compatible with a viral etiology. In our estimation, the genital herpesvirus (HSV-2) virus ranks highly as a candidate for this relationship, although the Nobel Committee prematurely awarded their prize for the human papilloma virus (HPV) as the cause of cervical cancer.

Prof. Aurelian was kind enough to add some additional remarks on the HSV-2 virus, its character, behavior, and interactions with humans that strongly support the virological, immunological, epidemiological, and clinical evidence favoring its unique role in the etiology of cervical cancer.

CHAPTER SEVEN

CERVICAL CANCER, INTERCOURSE, AND HSV-2 INFECTION

BACKGROUND

Uterine cancer was one of the most frequently observed malignant neoplasms in Western Europe during the 19th century. For example, it accounted for nearly one third of cancer deaths in Paris between 1830 and 1840. Physicians of the time regarded the cervix as the primary anatomic site of uterine tumors in the majority of cases (Moscucci 2016,15-46). In discussions on the pathogenesis of cervical cancer, they dismissed a number of factors subsequently demonstrated to be etiologically associated, viz. neither dissoluteness nor chastity, sterility nor fecundity, healthy pregnancies or the contrary, the habit of suckling… regular or irregular menstruation…abortion…hereditary influence, temperament, scrofula, syphilis, leucorrhea, the existence of polyps or fibrous tumors, appear to exercise the smallest influence on the development of uterine cancer.

Sauter of Constance is credited with performing the first hysterectomy by the vaginal route in 1821. The introduction of general anesthesia in 1846 made abdominal hysterectomy feasible and, as a result, diseased organs became available for systematic pathologic study. Knowledge regarding the pathogenesis of cervical cancer began to accumulate at a steady rate thereafter. Some of the etiological theories rejected

in the past, such as viral ("animalcule") etiology, sexual excess, syphilis, multiple pregnancies, and chronic cervical irritation, were resurrected as potentially viable theories during the 1950s and later years.

One recurring theory held that cervical neoplasia was in some way related to the intermitting and periodic variations to which the functional activity of the uterus is liable. This was empirically tested in 1842 by Rigoni-Stern of Padua in an early application of the epidemiologic method for neoplastic disease. Utilizing municipal records, he analyzed cancer mortality in Verona between 1760 and 1839, and observed an inverse relationship between the two commonest cancers in women: breast cancer was substantially more frequent among the unmarried women and religious sisters, but uterine cancer was rare among them in comparison with married or widowed women. The frequency of uterine cancer increased to a maximum at 30–40 years of age and declined substantially after age 60. This led Rigoni-Stern to speculate that the susceptibility of the uterus to cancer might vary with the "natural exercise of its functions." (Rigoni-Stern, 1842, 507-517). From these data, as well as from the gynecological literature of Rigoni-Stern's era, it is likely that cervical carcinomas comprised the preponderance of uterine cancer cases.

A possible relationship between neoplasia and chronic irritation or trauma was suggested by Broussais in 1826 and supported by Virchow in 1863. The trauma theory as it applied to uterine, i.e. cervical, cancer implicated recurrent lacerations, abrasions, and infections associated with poor obstetrical care or with multiparity as causal factors. This afforded one explanation for the general observation that

women in the lower socioeconomic classes experienced a disproportionately high risk of this disease.

A paradoxical exception to the trauma theory was posed by Jewish women of the time, as observed by physicians throughout Western Europe and the United States. In reviewing clinical material from 1893 to 1906, a New York City gynecologist noted that cervical cancer was 20 times more frequent among non-Jewish patients as compared with Jewish patients. In his own words: "When one stops to consider that of the total number of the Jewish women had badly lacerated cervices, that they were all immigrants who show a much greater predisposition to cancer than did the natives, and that they were living in the worst possible hygienic surroundings amidst the greatest squalor and privation such as obtain in the lower east side of the Metropolis, it is truly remarkable that so few cases of cancer of the cervix were detected among them" (Vineberg, 1919, 1223)

The relative infrequency of cervical cancer among Jewish women at the turn of the 20th century was attributed to observance of Mosaic Laws on sexual intercourse, to genetic factors, or even to ritual dietary practices. Surprisingly, the role of circumcision was not seriously considered until 1935 when Handley delivered a lecture on cancer prevention at the University of Liverpool and alluded to a visit he made to the Fiji Islands, where he noted that cervical cancer was substantially less prevalent among native Fijians than among resident Indians. He suggested that the relative freedom of Jewish women from cervical cancer might be due "to the protection which the hygienic operation of circumcision… affords against mixed bacterial infections of the cervix during coition" (Handley 1936, 987-991; Handley 1947, 841).

Across the Atlantic, at about the same time, the routine collection of cancer statistics from a geographically defined population was inaugurated, with the establishment of the Connecticut Tumor Registry in Hartford, Connecticut. This made possible the generation of useful information concerning time trends in cervical cancer mortality and incidence, as well as valuable analytical data. Another major landmark in the advance of knowledge on cervical neoplasia was the publication in 1943 of the monograph by Papanicolaou and Traut on the utility of exfoliative cytology in the clinical setting. Within a decade, Pap testing was being accepted and practiced by increasing numbers of American women, and carcinoma in situ came to be recognized as a neoplastic condition of clinical and epidemiologic significance.

Between the early 1950s and the mid-1960s, a number of interview-based epidemiological studies were directed at the role of sexual, marital, and penile factors in cervical neoplasia. While these failed to implicate circumcision as a significant factor, they did point to the relationship between the disease and a complex of sexual factors. A promising theory advanced in the refinement of the sexual or venereal hypothesis in cervical carcinogenesis took place in the late 1960s with the accumulation of evidence that the venereally transmitted herpes genitalis virus was causally associated with cervical cancer, and confirmatory evidence respecting the validity of the herpesvirus hypothesis mounted steadily over the following two decades (Kessler 1974a, 1091-1110; Kessler 1974b, 172-184; Kessler, Kulcar, Rawls, Smerdel, Strnad, and Lilienfeld 1974a, 369-376; Kessler, Kulcar, Zimolo, Grgurevic, Strnad, and Goodwin 1974b, 51-60; Aurelian, Jariwalla, Kessler, and Ts'o 1980, 81-99; Aurelian, Manak, McKinlay, Smith, Klacsmann and Gupta, 1981, S56-S87; Aurelian and Kessler, 1985, 235-248). More recently,

evidence was offered that the human papilloma virus (HPV) was the cause of cervical cancer and, for reasons noted below, a Nobel Prize was awarded to the proposer of this theory.

Mortality from cervical cancer has fallen dramatically in the United States since the early 1950s, among both white and non-white women in all age groups. The latter are at a considerably higher risk of death than white women and, despite their substantially higher inherent risk of the disease, they have benefited equally with white women in respect to improvement over time in declining mortality rates. Since the benefits are equivalent in both racial groups, it is unlikely that they stem from changes in socioeconomic status, access to medical care, education, or other sociodemographic factors. Rather, they are more likely due to exfoliative cytological screening, which was quickly adopted by a large majority of women over time. One can speculate that the spectacular decline in cervical cancer mortality might be attributable to advances in therapeutic modalities, but with no evidence for improvements in case fatality or survival among cervical cancer patients in specific histopathological stages, the truth is that a shift in the distribution of patients, with more and more being detected and treated earlier, in the more treatable stages of their disease, is responsible for the trend over time.

The case mix by clinical stage of cervical neoplasia patients has changed dramatically over the past decades: carcinoma in situ has increased dramatically in all classes of women, especially among younger women in all racial groups. The reasons are: (1) changing diagnostic practices among physicians, with cases previously diagnosed as severe dysplasia now being increasingly labeled as carcinoma in situ, for a variety of legal and medical practice-related reasons; (2) the almost universal proportion of women now undergoing regular or

episodic Pap testing; and (3) exposure of more and more American women to the presumptive etiological risk factors. We believe that the most likely of these is infection by the herpes genitalis virus, though the Nobel Committee voted in favor of HPV. While there remains some doubt about the specific agent, the social cause seems definite: a spectacular rise in sexual promiscuity, especially involving casual encounters with sexual partners from widely different geographical and social origins.

Although data on the true incidence of cervical cancer, or any other chronic disease, is usually immeasurable because of the shortcomings of cancer registries, some information of value may be extracted from them, nevertheless. We used such data from the International Agency for Research on Cancer to classify a number of countries and cities around the world in terms of cervical cancer incidence. One country stood out as having the very lowest rate: Israel, with a rate of 6 per 100,000 adjusted to the European "standard population." While much of the variation in rates reflects each particular cancer registry's method of collecting data, it seems clear to us that Israel's population is protected to some extent against cervical cancer, when compared with the other populations. This suggests a sexual or coital factor that would be consistent with their sexual mores, and protection by circumcision against a venereal virus such as genital herpesvirus (HSV-2) or HPV.

DESIGN

Much information has been assembled on relationships between cervical cancer and coital factors such as marriage, early marriage, pregnancy, promiscuity, prostitution, and concomitant venereal disease. Our interest in this disease

arose from the virological research of my wife and colleague, Prof. Laure Aurelian, who initiated basic science research on the HSV-2 viruses and became one of the world's most published experts in all aspects of these DNA viruses. Certain aspects of her research, in which the two of us closely collaborated, will be described here (Kessler 1976b, 783-792; Kessler 1976c, 38-47; Kessler 1977a, 1912-1919; Kessler 1977b, 84-87). One of our studies, termed the ManCan study, was designed to provide a reliable answer to the following question: What is a woman's risk of developing cervical cancer if she marries a man whose previous or subsequent wife has this disease? The design of the project is presented in Study Profile 1.

Study Profile 1

THE MANCAN STUDY

Probands
All cervix cancer cases in region
1950–1969, invasive and in situ

Husbands
All husbands of probands
prior to cancer diagnosis

Other wives **Controls**
All other wives of proband
Random women similar in husbands, previous and subsequent age, race, years of marriage, and prior marital status to other wives; selected from marriage records

Prospective follow-up
To death: ascertain cause
To survival: interview and Pap test

The ManCan study began with the identification of several thousand women with invasive or in situ cervical carcinoma diagnosed between 1950 and 1969 at the Johns Hopkins Hospital, who were designated as the study probands. Their husbands, at or prior to the time of cancer diagnosis, were identified, and all other wives of these husbands—previous and subsequent—were followed prospectively for the development of cervical cancer. For each "other wife," a control woman similar in age, race, years of marriage, and prior marital status was randomly selected from marital records of the geographic area and followed in similar fashion.

This study required a rather intensive follow-up staff because hospitals do not usually remain in communication with their patients long after treatment. We had already begun to consider setting up a statewide rapid-reporting cancer registration system to facilitate long-term studies, but this did not occur in time for the ManCan study. Patient follow-up ended after 1,889 "other-wife" probands and 1,626 matching control wives had been assembled and traced up to a given point in time. The results suggested that women marrying men whose previous wives had cervical cancer incur a risk approximately 2.5 times greater than normal for developing the disease themselves. Abnormal Pap tests were diagnosed in 13.6% of the other wives versus 8.4% of the controls. Marital clusters of cervical cancer befell 55 probands versus 22 controls. The results of the study added to the evidence that an important causal component of cervical cancer was venereal in nature, and therefore was compatible with a viral etiology.

The observed relationships of cervical cancer to coitus, circumcision, venereal disease, and prostitution led a number of investigators to suggest the possibility of a venereally transmitted etiology. The hypothesis remained conjectural until 1968 when Rawls, Tompkins, Figueroa, and Melnick (1968, 1255-1256) isolated HSV-2 from smegma specimens of four young men being treated in a venereal disease clinic. Shortly thereafter, Naib, Nahmias, Josey, and Kramer (1969, 940-945) observed the development of cervical carcinoma and squamous atypia in nearly a quarter of biopsied cervices, which had previously shown cytologic evidence of active herpetic infection. At about the same time, a series of sero-epidemiologic studies designed to measure neutralizing antibodies to HSV-2 in women with and without cervical neoplasia were undertaken. Despite the diversity of methodological approaches employed for these studies, a positive association between HSV-2 antibody prevalence and cervical cancer was confirmed.

The role of smegma as a cervical carcinogen would be consistent with the circumcision hypothesis, as well as with an increased risk of penile carcinoma among uncircumcised males. However, experimental studies in animals have generally failed to demonstrate the induction of cervical cancer by injection of human smegma. Chemical agents, such as coal tar derivatives used as vaginal douches, have been studied as potential cervical carcinogens, with equivocal findings. But squamous cell carcinomas have been experimentally produced by applications of 3,4-dibenzpyrene and methylcholanthrene. Trichomonas vaginalis and HPV have also been explored and, as noted above, HPV was designated as a cause of cervical cancer by the Nobel Prize Committee.

In their paper, Rawls et al. (1968, 1255-1256) failed to isolate the virus from the smegma of the husbands of 22 women with cervical cancer. However, the work of other investigators has generated evidence that males may serve as a reservoir of HSV-2, rendering them capable of transmitting the putative carcinogen to their coital partners. Centifanto, Drylie, Deardourff, and Kaufman (1972, 318-319) isolated HSV-2 from prostate, vas deferens, and urethra specimens of 15% of 190 male urology clinic patients. The urethral discharges of two other groups of men attending venereal disease clinics because of nonspecific urethritis also yielded HSV-2. However, no virus could be detected in 144 cultured vas deferens specimens of patients undergoing vasectomy. HSV-2 has also been isolated from the urinary sediment of women with known herpetic infections (Kessler and Aurelian 1975, Chapter 11; Kessler 1978b, 211-229; Jariwalla, Aurelian, and Ts'o 1980, 2279-2283; Kessler 1979b, 790-794; Kessler 1981, S7-S24).

Indirect evidence favoring an etiologic role for HSV-2 in human cervical carcinoma is also abundant. The virus itself is venereally transmitted, as demonstrated by clinical studies, virus isolations, and seroconversions. Squamous carcinoma of the cervix behaves as a venereal disease: it is most prevalent among prostitutes, the sexually promiscuous, women marrying multiple times, and those who initiate coitus at a young age. But it is virtually absent in virgins and children, among whom only cervical adenocarcinomas have been reported.

The risk of cervical cancer also appears to be correlated with that of penile cancer in associated males, a phenomenon reported in both Puerto Rico and Japan. The disease is frequently diagnosed in patients with a variety of other venereal diseases, including syphilis, gonorrhea, and

trichomoniasis. The transmissibility of cervical cancer is also suggested by the results of our ManCan study, which demonstrated a disease risk enhanced severalfold among women marrying men who were previously associated with cervical cancer cases.

ANALYSIS

Substantial advances on the pathogenesis of cervical cancer accrued from the work of Prof. Aurelian and her basic science coworkers, of which some of the most promising are reported here. She posited the fundamental questions, designed the appropriate studies, and came tantalizingly close to producing a proven etiological role of HSV-2 in human cervical cancer. She demonstrated the presence of HSV-2 antigens in exfoliated cervical cancer cells, and the release, under specific conditions, of HSV-2 virions and infectious virus from biopsied cervical cancer tissue. Aurelian and her colleagues identified and isolated a viral antigen that she named "AG-4" in cervical cancer tissues. She revealed that this antigen represents a virus protein (ICP10-PK, also known as LA1 oncogene), which ancestrally was co-opted by the virus from a cellular gene, modified, and integrated into the large subunit of HSV-2 ribonucleotide reductase and has its own protein kinase activity. This fusion of ICP10-PK with the large ribonucleotide reductase subunit creates a unique gene, which is only present in HSV-2 and is not found in the other human herpes simplex virus, HSV-1. She also demonstrated that ICP10-PK regulates cellular DNA replication through the activation of canonical cellular pathways and causes the neoplastic transformation of normal cells, strongly demonstrating the potential carcinogenicity of the genital herpesvirus. This shows that ICP10-PK converts normal cells, which have a limited life-span, grow in a two-dimensional

pattern, and do not cause tumors in animals, into cells that have acquired unlimited replicative potential, grow in three-dimensional patterns, and cause tumors when injected into animals.

Prof. Aurelian's studies also demonstrated that ICP10-PK is associated with the active growth phases of cervical tumors and is absent in healthy women. Women with a variety of other cancers, including cervical adenocarcinoma, fail to test positive for AG-4/ICP10-PK. More than 90% of women with untreated invasive squamous carcinoma of the cervix are positive for AG-4/ICP10-PK. They become negative a month or so after surgery or radiotherapy for the disease and positive again after its clinical recurrence. Approximately two out of three women with documented carcinoma in situ are also AG-4/ICP10-PK positive, and we suspect that the remainder are women whose lesions are either misclassified or are otherwise destined to regress. Approximately one woman in three diagnosed as having cervical dysplasia tests positive for AG-4. In our view, this is the type of patient whose lesions are programmed for eventual malignant transformation; the remaining two thirds will, in all likelihood, regress (Jariwalla, Aurelian, and Ts'o 1979, 404-409; Aurelian, Jariwalla, Kessler, and Ts'o 1980, 81-99; Aurelian, Kessler, Rosenshein, and Barbour 1981, 455-471; Jariwalla, Aurelian, and Ts'o 1983, 5902-5906; Sharma, Nelson, Smith, and Aurelian 1994, 23-28; Smith, Yu, Kulka, and Aurelian 2000, 25690-25699; Smith, Nelson, Gober, Aurelian, and Goswami 2000, 10417-10429).

"AG-e," another structural component of the genital herpesvirus, was also discovered by Aurelian and her team (Smith and Aurelian 1979, 255-260). This herpes-specific antigen was shown to be the virus-encoded major-DNA-

binding protein that is involved in DNA unwinding. It is present in exfoliated cervical anaplastic cells but not in normal cells, and it induces a transient cell-mediated immune response. Healthy women are nonreactive, which thus suggests another potential way to screen for the disease. It may also be significant that both the viral ribonucleotide reductase and the major-DNA-binding protein are involved in DNA replication/regulation, and that ribonucleotide reductase has been associated with a mutator phenotype.

Cancers have also been induced by several varieties of herpesviruses in a number of animal models, including frogs, rodents, and fowl. Furthermore, HSV-2 causes cancer of the mouse cervix, a process that can be prevented by prior immunization with HSV-2. Burkitt's lymphoma and nasopharyngeal carcinoma in humans are closely linked to a related virus, the Epstein-Barr virus. Finally, the latency phenomenon, which typifies the biological behavior of herpesviruses, is regarded as enhancing the malignant potentialities of the virus.

Overall, HSV-2 fits the model of a carcinogen for the human cervix extremely well (Aurelian, Manak, McKinlay, Smith, Klacsmann, and Gupta 1981; Kessler 1984, 1-20; Kessler 1986, 55-64; Kessler 1987c, 57-75). It is prevalent throughout the world and is venereally transmitted. Infections may be acute and symptomatic, as well as clinically inapparent; a significant characteristic in view of the evidence that latent persistence of the viral genome is conducive to malignant transformation. Tumors in a number of animal species have been associated with herpesvirus strains, and at least two other human neoplasms—nasopharyngeal carcinoma and Burkitt's lymphoma—are serologically related to infections

by this virus. HPV, crowned as the cervical carcinogen, does not measure up in most of these relationships.

DISCUSSION

We continue to believe that the herpes genitalis virus comes closer to satisfying the modified Koch's postulates of etiology for cervical cancer than any other putative human viral carcinogen. This is not to suggest that the virus is an absolutely sufficient cause of the human disease in its own right. There may well be synergists, cofactors, adjuvants, or other agents that render a woman susceptible to the herpes-induced carcinogenic process. In fact, HSV-2 is a unique carcinogen in that it can act at various stages of the neoplastic process. It is capable of immortalizing normal diploid cells, an early stage in carcinogenesis, which can be converted to a neoplastic phenotype by other cofactors possibly including HPV. HSV-2 can also convert cells immortalized by other factors (chemical or viral) to a neoplastic phenotype. Finally, HSV-2 can both immortalize and neoplastically transform normal diploid cells, further suggesting its significant role in human carcinogenesis.

Estrogenic hormones are a likely cofactor in cervical neoplasia. Such steroids affect the growth characteristics of HSV-2 in tissue culture. Furthermore, during the course of our case–control study in Yugoslavia, we observed significant differences in menstrual histories between subjects with and without cervical cancer. Cases tended to have more "normal" menstrual histories with relatively few long, heavy, painful, or irregular cycles, as compared with controls. The fact that cervical carcinoma and carcinoma in situ may be increased among women who use oral contraceptives supports this notion. At the same time, the selective factors operative in

studies on women utilizing one or another contraceptive mode should not be ignored. Specific estrogenic and progestational receptor activity has been detected in normal cervical squamous epithelia, as well as in cervical intraepithelial neoplasms.

Evidence for an etiological relationship of cervical cancer with HPV seems much sparser to us. Although a clinician is more likely to observe evidence of condyloma on a human cervix with or without cervical cancer than active genital herpes lesions—because of the chronicity of papillomatous lesions and the latency which is characteristic of genital herpes infections—the weight of evidence favoring HPV still is based on studies using DNA derived from an invasive cervical cancer, rather than from an unequivocally proven HPV. The histological evidence of HPV infection in cervical cancer is almost solely based on morphologic, i.e. nonspecific, criteria. Seroepidemiological evidence and evidence from temporal relationships of the two conditions are absent. Koilocytosis is accepted as a cytopathic effect of HPV, even though the virus cannot be detected in half the cases. Finally, the HPVs that have been associated clinically with cervical cancers do not cause neoplastic transformation of cells in vitro. In a recent study, however, a recombinant HPV 16 DNA was shown to cause neoplastic changes in immortalized NIH 3T3 cells, as well as tumors in immunologically incompetent mice. The relevance of these findings to the in vivo situation is as yet unclear.

Lurking in the background for me as a practicing epidemiologist is the thought that, while the biologic and clinical evidence clearly favors HSV-2 as the likeliest cervical carcinogen, the fact that nonmalignant papillomatous lesions are so commonly found adjacent to the cervix in many

gynecological patients greatly influences the judgment of many gynecologists to discount the objective scientific evidence for HSV-2 in favor of HPV, which lacks much of the scientific proof but is frequently observed as being in the right place at the right time. To date, there is little evidence of a decline in the incidence of cervical cancer as a result of widespread HPV vaccination, and, consequently, the scientific basis for the Nobel Committee's conclusion that HPV is the cause of cervical cancer still awaits confirmation.

As of this time, one may ask whether there are any alternative venereal explanations for the herpesvirus hypothesis in the pathogenesis of cervical cancer. Sperm, smegma, chemical substances, and protozoa have all been suggested as factors or cofactors in cervical carcinoma. The importance of metaplastic changes in the transition zone of the cervical epithelium during adolescence and at the time of first pregnancy have also been emphasized. Active cell growth with phagocytosis, pinocytosis, and nucleic acid turnover characterize these time periods, during which vectors of DNA—such as the sperm—might theoretically function as mutagens. It is the basic proteins of the sperm head, especially the protamines that have been postulated as agents of human cervical cancer. The evidence for this, still rather tenuous, is that the ratio of protamines to histones in sperm ejaculates varies by social class, being substantially greater in the lower socioeconomic groups that are at a higher risk of cervical carcinoma.

While this volume is devoted to discussions of disease pathogenesis from an epidemiological perspective, the commentary of Prof. Aurelian, an eminent virologist and immunologist who has devoted many years to the study of the herpesviruses, greatly strengthens the evidence for a causal

role of this virus. While her observations stem directly from her scientific expertise, the reader should also not fail to notice her unique understanding of classical epidemiological principles acquired during a half century of cohabitation with an unapologetic spouse devoted to this field.

My purpose in including her commentary is to exemplify the enormous value of biomedical scientists working in concert with classical epidemiologists to advance knowledge and control disease. There is an enormous need to encourage this approach in all of medicine.

The following several paragraphs reflect Prof. Aurelian's secondary comments in her own vernacular on the relationship of the HSV-2 virus to human cervical cancer. The disease, long recognized as sexually transmitted, is manifested by preinvasive lesions that often occur decades before the invasive lesions. The DNA of this virus persists in human tissues without killing the tumor cells through virus replication. HSV-2 produces chromosomal aberrations similar to those described in cervical cancer, and antigens found in tissue-cultured cells infected with HSV-2 are detected in human cervical cancer cells.

Basic scientists have considered three possible explanations for an association between HSV-2 and cervical cancer. The first of these, **the preferential hypothesis**, argues that the virus preferentially infects neoplastic cells, so that viral infection occurs *after* the development of the neoplastic lesion. We have studied the presence of HSV-2 antibodies in patients with preinvasive and invasive cervical cancer, and have observed virtually identical frequency rates, which thus argues against this hypothesis.

Defenders of the preferential hypothesis have argued that we used an unreliable marker for HSV-2 detection, which failed to differentiate between HSV-1 and HSV-2. However, this is unlikely, because we later used a serological assay employing an IgG immunoglobulin, which can specifically differentiate between HSV-1 and HSV-2, in order to measure the AG-4 activity, and showed that AG-4 was specifically recognized by the HSV-2, but not HSV-1, antibody. Indeed, AG-4 was later identified to be ICP10-PK, which is present in HSV-2 but not in HSV-1.

A second explanation is **the promiscuity hypothesis**, which proposes that the association of HSV-2 with cervical cancer is simply the result of the sexual promiscuity of the cervical cancer population, which is the likeliest to suffer from a multitude of sexually transmitted diseases. However, our studies found no association between cervical cancer and any other sexually transmitted disease.

The third—and, in our view, the likeliest—explanation for the association between HSV-2 and cervical cancer is **the causation hypothesis**, which proposes that virus gene(s) expressed independently of virus replication are responsible for the increased cell proliferation. Indeed, ICP10-PK is expressed with immediate early kinetics, i.e. before and independent of the expression of any other viral genes, and it causes neoplastic transformation. The tumors further develop from the secondary effects on the course of differentiation and evolution of the new transformed cell type. Our concept is that the virus does not replicate in cytopathologically abnormal cells and that they do not contain virus structural components, but rather that they express the transformation-inducing protein ICP10-PK early in tumor development, i.e. in preinvasive lesions (Aurelian and Kessler 1985, 235-248;

Kessler 1987a, 57-75; Kessler 1987b, 195-197; McCarter, Kessler, and Comstock 1987, 195-205; Kessler 1989, 3-10; Kessler 1990a, 1-25; Kessler 1990b, 1-11).

In this context, the possibility cannot be excluded that both sexually transmitted viruses, HPV and HSV-2, contribute to cervical carcinogenesis. This interpretation follows on the finding that HPV does *not* cause neoplastic transformation, characterized by uncontrolled cellular DNA replication and three-dimensional cell growth, but that it can alter normal cells by rendering them immortal. It argues that HPV may provide an initiating step in the process of carcinogenesis, in which normal cells are immortalized, and that this is followed by HSV-2 ICP10-PK-induced, activation of transforming canonical pathways that impart neoplastic potential and onset of tumor formation.

Chapter Eight Summary

Diethylstilbestrol and Vaginal Cancer in Young Women: A Misguided Decision that Aroused the Public

The diethylstilbestrol (DES) controversy is a prime example of questionable epidemiologic conclusions being publicized, inaccurately portrayed in the news media, and superficially reviewed by government health agencies, resulting in extraordinary public anxiety among millions of young women, their mothers and fathers. Major lawsuits were one result and ultimately the FDA banned the drug without substantial evidence.

I did not undertake a study on this topic because the evidence seemed so inadequate, but I did participate in governmental reviews on the issue. My conclusion was that the controversy should become an important teaching tool in the public health schools and medical school departments of public health.

In the late 1960s, an unprecedented manifestation of a rare cancer was noticed in young women. Clear cell vaginal cancer was diagnosed in a younger age group than ever seen before. A possible link to DES was suggested in 1971, but the FDA took no action until public pressure, including Congressional hearings, led to a warning and, thereafter, to a total ban in 2000.

Herbst and his colleague noted seven cases of vaginal cancer in the records of two hospitals between 1927 and 1963 (Herbst and Scully 1970, 745-757;). Clinical reports such as these usually suffer from a variety of methodological problems that are not easily resolved. Incomplete documentation, reliance on old diagnostic specimens that cannot be rectified , the inability to validate the diagnoses, the absence of details on DES use, hospital selectivity, and the futility of seeking risk factors by reviewing records not designed for this purpose are among the problems.

The government's actions in this matter, as well as alternative pathways, are well worth reviewing in the nation's public health schools and medical school departments of public health.

CHAPTER EIGHT

DIETHYLSTILBESTROL AND VAGINAL CANCER IN YOUNG WOMEN: A MISGUIDED DECISION THAT AROUSED THE PUBLIC

BACKGROUND

The diethylstilbestrol (DES) controversy is a prime example of epidemiological conclusions of questionable validity articulated, inaccurately portrayed in the news media, and superficially reviewed by US government health agencies for many years, eventually leading to extraordinary public anxiety in millions of young women and their mothers. Over the long run, this controversy raised major lawsuits and, ultimately, the withdrawal of the drug by the federal government without solid evidence. I decided not to undertake a study of DES because the proffered evidence was so unimpressive, but I did participate in governmental and academic review bodies that evaluated the issue at various times during its long tenure in the public's attention.

The drug was created as a synthetic estrogen in 1938 and was prescribed to treat menopausal symptoms. It was approved by the FDA in 1947 as a preventative for miscarriage until 1971, when it was withdrawn from the market. In 1966, it had been banned by the FDA for use as a stimulator of chicken growth and for abnormal male breast development in humans.

In 1971, DES was implicated in the occurrence of cancer in a small number of young women reported by Dr. Arthur Herbst and colleagues (Herbst, Ulfelder, and Poskanzer 1971, 878-881). The neoplasm, a clear cell cancer of the vagina, was diagnosed for the first time in these women, with a causal link to the intake of DES. The FDA took no action until public pressure, Congressional hearings, testimonials from the women's parents, and other political pressures forced it to issue a warning in November of that year. In the following year, DES use was constrained for pregnant women and, finally, in September 2000, the FDA withdrew its approval for any human use.

The enormous pressure favoring the DES ban was initially exerted by the parents of a handful of cases, leading swiftly to millions of women and children being petrified by inaccurate, disorganized, and largely unscientific news reports, frightening state and local governmental warnings, and the tearful stories of mothers who presumably had lost their daughters to DES exposure. Much of the national hysteria was aroused by a non-profit consumer group, DES Action, established in 1980 and still active 40 years later. It is this organization that publicized innumerable false notices about diseases caused by DES, beginning with vaginal cancer and later including, inter alia, breast cancer, infertility, and depression in women and testicular cancer, coronary heart disease, and diabetes in men.

In February 2011, the FDA communicated to Senators John Kerry and Scott Brown about the "devastating health consequences of DES," discussed initiatives to prevent future drug disasters, and openly described DES use as a "tragedy" (NIH Intramural Research Program, 2011). This information was circulated throughout the United States over a sustained period of time, and eventually panicked millions of young

women and their parents. The legislative and executive branches of the federal government and its regulatory agencies then felt obliged to allay the public concern: DES—after more than 30 years of intensive debate, without any revision of scientific knowledge about its safety—was finally banned for human use.

While the artificial sweeteners saccharin and cyclamate continue to be sold to this very day despite mandatory federal warnings about risks of cancer and other ailments, it is instructive to review the regulatory process undergone by DES, beginning with its initial use as an uncontroversial drug to help sustain pregnancies in women, and ending in a highly controversial political scandal following publication of a single paper on a few vaginal cancer cases. The initial report, supplemented by a small number of poorly designed additional studies, led to government regulation, an alarmed public, and, three decades later, a total ban.

DESIGN

Herbst et al. (1971, 878-881) abstracted the records of the Massachusetts General Hospital and the Pondville State Cancer Hospital to identify cases of primary carcinoma of the vagina diagnosed between 1927 and 1963. There were 68 cases identified, none below 24 years of age. This type of uncontrolled clinical review, often referred to in the press as "an epidemiological study," usually suffers from serious methodological and inferential problems that obfuscate, rather than elucidate, the clinical facts. The shortcomings in this analysis included: (1) a dependence on incomplete documentation and the use of diagnostic specimens over a 40-year time span that cannot be rectified; (2) the impossibility of validating the diagnoses and details of DES use through

(unavailable) supplementary medical data sources; (3) hospital selectivity (as to whether younger or higher cancer risk patients were referred to other hospitals); and (4) the futility of searching for etiological risk factors by reviewing hospital records not designed for this purpose.

The Herbst group followed up their clinical review with a second study at the same hospitals, of seven vaginal cancer cases below age 23 that were treated between 1966 and 1968. Histologically, the neoplasms were adenomatous rather than epidermoid, and thus represented a possibly new genre of vaginal cancer, with the authors claiming "no such cases in the younger age group had been seen at this institution before 1966." (Herbst, Green, Ulfelder, 1970, 210-218). The sudden appearance of a relatively rare cancer in a hospital is certainly impressive, but its biological significance must be interpreted with great caution. For example, (1) the hospital may not have previously attracted post-pubertal, adolescent, and young adult females with gynecological problems; (2) changing clinical interests of the staff physicians may have resulted in an increasing emphasis on young patients; (3) if, as is true for a number of other cancers, vaginal adenocarcinomas differ in their distribution by race, ethnic group, or social class, then changes in the demographic characteristics of the populations served by the Massachusetts General and Pondville hospitals could explain a sudden increase in the incidence of a specific cancer; and finally (4) one must not ignore the possibility of "bandwagon effects" which sometimes follow clinical reports of the sudden appearance a rare "new" disease.

For example, when retrolental fibroplasia was first reported in the late 1940s, hospitals all over the world began to discover "cases" among newborns. Even more remarkably, retrospective analyses of medical records in the hospitals disclosed that

similar cases had been occurring for many years. That many of these clinical reports were fallacious or artifactual became evident when the condition was proven to be related to excessive use of oxygen in the premature nursery, a practice that had been recently introduced at that time. Thus, a number of reported "cases" occurred among unexposed infants who could not have had the disease! Whether such a "bandwagon effect" is operative with respect to vaginal adenocarcinoma in young women is unknown, if only because of the paucity of controlled studies ever undertaken.

Herbst and his colleagues attempted to put their findings into perspective by instituting a "controlled" study. They selected four controls for each of the eight diagnosed vaginal adenocarcinoma cases, interviewed the mothers, and reviewed the existing medical records. A "highly significant association between the treatment of the mothers with diethylstilbestrol during pregnancy and the subsequent development of adenocarcinoma of the vagina in their daughters" was noted (Herbst, Ulfelder Poskanzer 1971, *878-881).* This finding was statistically significant because, as it turned out, none of the 32 control mothers reported receiving DES.

It should be noted that DES exposure, or its absence, was ascertained by anamnesis and apparently without validation by medical records or physician testimony. It is likely that mothers of children who developed cancer would "recall" drug use during that pregnancy more readily than the mothers of normal offspring. The study should have been more appropriately conducted on controls hospitalized for serious diseases, which might have rendered them as sensitive or anxiety-laden as the mothers of the vaginal cancer cases.

ANALYSIS

As important as the question of differences in DES exposure between the two groups of mothers is the question of the *reasons* for the DES exposure. If, for example, mothers with a hereditary tendency to the development of vaginal cancer in their daughters required DES to sustain their pregnancies, the same differences would have been found in the absence of an etiological relationship between DES and vaginal cancer. While no evidence favoring this notion exists, there is considerable evidence from the study itself that the DES mothers differed from the control mothers in other ways than DES exposure alone. The most important of these were: (1) a substantially greater likelihood of a prior history of pregnancy losses, and (2) a history of bleeding during the pregnancy of interest.

In both of these indices of abnormal pregnancy histories, there were statistically significant differences between the case and control mothers. These differences could reasonably account for the administration of DES during the pregnancy, and could explain the observed findings on the basis of high-risk pregnancy characteristics, rather than exogenous DES administration per se. In other words, it may not be the DES but, rather, the reason that DES had to be administered which rendered a woman likely to produce offspring with vaginal adenocarcinoma. The fact that case–control differences in DES administration achieved smaller p values than those for prior pregnancy loss or pregnancy bleeding could reflect the very small sample size, as well as the greater likelihood that the control mothers were in endocrinologic balance and, therefore, not requiring exogenous hormone maintenance during gestation.

Herbst et al. (1971, 878-881) observed that "all the mothers who took stilbestrol began therapy in the first trimester of pregnancy." In subsequent papers, this was taken as evidence strengthening the DES etiology hypothesis because embryological development of the vagina occurs during the first trimester. However, an equally reasonable noncausal explanation is that threatened abortion, bleeding, and other pregnancy problems common during the first trimester would also require this type of hormone supplementation. In fact, the investigators themselves noted that "bleeding during this pregnancy or previous pregnancy loss (or both) led to the administration of stilbestrol in all seven cases" from the Massachusetts General Hospital.

In the eighth case, "there was no evidence that estrogens were administered during pregnancy nor had [the patient] experienced prior pregnancy loss or bleeding during the study pregnancy." The investigators attributed this cancer to factors other than DES; in other words, "these tumors were known to occur, though rarely, in women born before the availability of oral estrogens". Thus, factors other than maternal stilbestrol ingestion appear to be operative in their development. This may be regarded as additional evidence of the unique selectivity of the Massachusetts General Hospital patient population studied. While it is acknowledged that such vaginal cancers occurred in the past, the old records apparently failed to disclose a single case as far back as 1922. Furthermore, it was noted that "during this [1946 through 1951] interval there was a special high risk pregnancy clinic at the Boston Lying-In Hospital in which stilbestrol was prescribed to 675 ward patients, thus providing another mechanism for the non-random admission of patients to specific hospitals biased in terms of an a priori risk of certain diseases." It should be noted that no *systematic* searches of the

records in any of the other hospitals in Boston or elsewhere had yet been made in an effort to identify presumed DES-associated vaginal carcinomas in a nonselective and unbiased fashion.

A common associated finding in DES-exposed offspring is benign vaginal adenosis. Herbst et al. (1971, 878-881) opined that this "suggests that an anomaly of vaginal epithelial development may be a predisposing condition" for vaginal adenocarcinoma. While this conclusion may be valid, though as yet unconfirmed, it is important to recall that the prevalence of adenosis exceeds that of vaginal adenocarcinoma by many fold. Thus, it is unlikely that adenosis per se (or that an agent such as DES which may be associated with adenosis) is a vaginal carcinogen. Rather, it is likelier that (1) both vaginal cancer and vaginal adenosis are secondarily associated with DES, i.e. the diseases occur in the offspring of women otherwise predisposed to them who, for related reasons, also require hormone support during their pregnancies; or (2) there is an as yet unidentified congenital, hereditary, or environmental agent that triggers the transformation of vaginal adenosis to carcinoma. It is for the elucidation of such factors that further studies are needed.

The fact that "the time of birth of these patients [1946–1951] coincides with the beginning of the widespread use of estrogens in support of high-risk pregnancy" (Herbst, Ulfelder, and Poskanzer 1971, *878-881)* is nothing more than a correlational statement. Many things began to increase in the early postwar period, in addition to vaginal adenocarcinoma and estrogen therapy in high-risk pregnancies. Among these were ingestion of artificial sweeteners, exposures to television sets, etc. which obviously have nothing to do with vaginal cancer. These examples demonstrate the speciousness of

many statistically significant correlations that are uncritically reported in the print and public media.

Following the publication of their original observations which, for all the inferential problems, are still fascinating, Herbst et al. chose not to initiate a series of well-designed and controlled epidemiologic studies to confirm the DES etiology hypothesis. Rather, they established a Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females for the purpose of soliciting the assistance of physicians in registering information on clinical cases of vaginal (and, later, cervical) adenocarcinoma among young women. Public solicitations of this kind are highly subject to selective biases. First of all, since the imputed relationship between DES and vaginal cancer was highly publicized from the outset—both by the authors and the federal government—cases known by physicians to be associated with DES exposure would almost certainly be registered more frequently than those without such exposure. This would occur despite the fact that the registry officially requested the registration of all vaginal and cervical cancers among young women, regardless of prenatal DES exposures.

A second factor predisposing to selection biases is the reliance of the registry upon an essentially passive, rather than active, registration system. No mechanisms were established to systematically review the records of all hospitals, pathology departments, oncology centers, radiology practices, etc. to identify the total incidence and prevalence of genital cancers among young females in a given geographic area. Instead, the registry waited for the physicians themselves to submit such reports, encouraged perhaps by solicitations in medical journals and by direct mailings. In our experience, busy medical practitioners are unlikely to take the time—or even to

have the time—to submit research reports unless there exists a specific incentive. The discovery of vaginal cancer in a young patient whose mother was exposed to DES would provide such an incentive, if only because of the medico-legal implications and the public interest.

Some indication of the selective biases, which may be operative in the registry, may be derived from data reported by the investigators themselves. Herbst, Green, and Ulfelder, 1970, 210-218) identified the birthplaces of 60 vaginal and cervical cancer cases. Of the total, only 21% occurred among those born in New England, which constituted 6% of the US population in 1970. Unless DES use was three to four times more prevalent in New England than elsewhere, the registry—having been established in Boston—was manifestly more successful in attracting physician response locally than from elsewhere in the country. It would be interesting to learn how the proportional geographic distribution of cases may have changed since the registry moved to Chicago.

Most of the papers published on the DES and genital cancer association since the establishments of the registry have consisted of periodic reports on the characteristics of registered cases. Thus, in an early report, 91 cases were described. However, because of the registry's mode of operation, much of the requisite information was incomplete at the time of publication. For example, the pregnancy histories of the patients' mothers were obtained in only 66 of the 91 subjects. As selective as the registry cases must be in general, such a degree of incompleteness in case reports certainly compounds the problem of selective bias. Our opinion is that periodic registry reports ought to be published only after complete or near-complete information has become available on the cases registered up to a defined time.

The following type of comment frequently appeared in publications of the registry: “Recently, clear cell adenocarcinomas of the vagina and cervix in young females have been reported with increasing frequency.” The implication here is that the disease is relatively new and, therefore, that its relationship with DES (also fairly new) may reasonably be inferred. In fact, however, such comments are based mainly on the registry data and, perhaps to a small extent, on a few small, and uncontrolled, clinical reports of individual cases. The “bandwagon” effect in clinical reports of rare diseases has already been alluded to. This is commonly seen, for example, during officially announced “flu seasons,” at which time respiratory symptoms are attributed by physicians to “influenza virus” even when appropriate diagnostic tests to validate the diagnosis are lacking.

Another example of the incompleteness of the data upon which the published registry reports are based is seen in another paper where details on dosage and duration of stilbestrol therapy were made available for only 46 of the 91 cases. The absence of a relationship between DES dose and vaginal or cervical cancer risk in exposed women would argue against an etiological role for DES. The risks of cancer or teratogenesis generally increase with increasing exposure and decrease with decreasing exposure to the causal agents. Yet, vaginal cancers have been associated with exposures as small as 1.5 mg DES per day and as much as 150 mg DES per day, and with total dosages ranging between 135 mg and as much as 18,200 mg. This is not impressive evidence in favor of the DES etiology hypothesis. More definitive is the fact that no cases of vaginal cancer were reported after DES exposure later than the 18th week of pregnancy, i.e. the period coinciding with embryological development of the genital tract. Unfortunately, conclusive decisions must remain tenuous

because these are also the months when abortions, bleeding, and other pregnancy complications requiring hormone therapy are most likely to occur.

There may be evidence that prenatal DES therapy is associated with a relatively high prevalence of vaginal—though not cervical—adenosis, but the evidence is not as strong as it might be, because so few controlled studies have been undertaken. Such studies should involve representative groups of children and young women *not* exposed in utero to DES, who are undergoing genital tract evaluation.

Because so few cases reported to the registry involved prenatal exposures to steroidal estrogens, Herbst, Green, and Ulfelder (1970, 210-218) concluded that the non-steroidal drugs (such as DES) have properties associated with the development of these cancers not shared by steroidal estrogens. The implication that DES and its analogues may play causal roles in cervical and vaginal cancers of the young is not justified, however, in view of the highly selective nature of the cases reported to the registry. The investigators themselves admit that their interpretation may be erroneous, however, since it is not known how frequently steroidal estrogens have been used to support pregnancies. As for the absence of a dose–response effect, Herbst et al. conceded that factors other than maternal hormone administration are involved in the development of these carcinomas. The latter point is valid and should be emphasized.

The experience of 34 cases is compared with that of approximately 275 girls between the ages of 13 and 24 years who did not have a history of intra-uterine exposure to stilbestrol. The cytologic, clinical, and histopathologic examination procedures administered to the 34 exposed cases

are described in detail. Conversely, little is said about the procedures utilized in examining the 275 non-exposed girls except for the statement that in this group, 13 had punctate areas of red discoloration in the vagina and that these areas were biopsied. Was a Schiller test performed on all 275? Was a clinical examination of the vagina conducted in the non-exposed young women? Since such questions are not addressed by the investigators, their conclusions on the frequency of vaginal adenosis among the exposed and its rarity among the non-exposed remain unsubstantiated. Information is also not offered on the precise method utilized for selecting the 275 non-exposed girls, so that their comparability to the 34 study cases cannot be evaluated.

Cervical erosions were observed in 21 of the 34 exposed patients. The reader is not informed as to whether there were no erosions in the controls or whether they were simply not examined. In any event, coital practices may influence the development of cervical erosions. For example, herpes genitalis, trichomoniasis, and other sexually transmitted infections are often associated with cervical erosions. Therefore, in interpreting the apparently high prevalence among the exposed subjects, it would be essential to control for differences in sexual activity. The investigators' statement that "the fact that all but one of these 34 patients had never been pregnant suggests a congenital origin for the erosion" does not adequately address the issue.

A review article on the subject noted the failure to induce vaginal cancers in laboratory animals fed DES. This is explained on the basis of species differences so that, for example, thalidomide may produce phocomelia in the human, but the drug does not affect the fetal rat. And cortisone causes cardiac abnormalities in the rabbit but not in humans. This

argument is two-sided, however. For example, the U.S. FDA has relied heavily on extrapolation of animal results to humans in regulating potential human carcinogens (e.g. banning saccharin as a potential human bladder carcinogen).

The fact that carcinomas are extremely rare while adenosis is relatively common in the stilbestrol-exposed population raises an important question concerning the pathogenesis of vaginal cancer in young women. Such cancers might result from a triggering of adenotic tissue by still unidentified factors, whereas the adenosis itself may be directly related to DES exposure. Another possibility is that, although adenosis is related to DES, vaginal carcinomas are only secondarily related. The evidence for this is their occurrence in women who require estrogenic support during pregnancy because of high risks of bleeding, abortion, or other adverse outcomes.

In their paper, Herbst, Ulfelder, and Poskanzer (1971, 878-881) observed low serum progesterone levels as measured by radioimmunoassay in five young vaginal adenosis patients whose mothers had been exposed to stilbestrol during pregnancy. Because a clinical regression of the lesions was observed in the absence of epithelial changes, the investigators suggested that progesterone may exert an anti-inflammatory action, and that this, rather than its estrogen-antagonistic properties, may be responsible for the regression of the adenosis. However, if adenosis is closely related to steroid hormone levels, this would suggest that the DES–adenosis association may have the same explanation as the DES–vaginal adenocarcinoma association, i.e. women with tendencies to steroid hormone imbalance (and, accordingly, problems in early pregnancy requiring hormone therapy) would be the ones at risk of these conditions—without the need to presume a direct action of DES.

In another of their papers, it was observed that 82% of the cases were positive for the treatment of a high-risk pregnancy by diethylstilbestrol, which again raises the question of whether it is the DES that induces the cancer or whether it is the preexisting gynecological problem that incidentally necessitates DES therapy in pregnancy.

The youngest patient in their series of 170 was 7 years old and the oldest was 29. This is an extremely wide range for cancer attributable to prenatal carcinogen exposure. Specific carcinogens tend to be associated with relatively specific latency periods, which precede the clinical manifestations of the tumor, at any given dose of the carcinogen. In the present instance, there is, first of all, no dose–response effect whatsoever and, secondly, the latent period is highly variable. In any event, the occurrence of vaginal carcinoma in a 7-year-old premenarchial girl is not consistent with Herbst's theories concerning the pathogenesis of DES-associated neoplasms. In fact, of the 16 patients in the registry series who were 12 years of age or younger, only 8 had histories of prenatal exposure to stilbestrol (Herbst and Scully 1970, 745-757; Herbst, Green, and Ulfelder 1970, 210-218; Herbst, Ulfelder, and Poskanzer 1971, 878-881).

CONCLUSIONS

The 50-fold variation in total DES dosage, the greater than 100-fold variation in maximum daily dosage, and the variation in total duration of therapy from seven days to nearly nine months pose formidable problems to those who argue in favor of a straightforward etiological relationship of prenatal non-steroidal hormones to the subsequent development of vaginal or cervical cancer in young women.

Our detailed review of the papers by Herbst and his colleagues on the DES issue is designed to point out the many epidemiologic factors that can affect conclusions in clinical studies. In no way is it meant to reflect adversely on an eminent biomedical researcher whom I highly respect, whose work I followed closely with admiration, and with whom I interacted on a number of occasions. The reliance of biomedical investigators on clinical and historical attributes of their patients is an asset at a time when detailed knowledge of agents, hosts, and environments of disease is increasingly regarded as secondary in importance to the patient's genome, heredity, and computer-generated factoids. I would argue, in addition to the patient and the laboratory, epidemiological reasoning must remain an essential part of the analytical approach in medicine and public health. Clinically trained students in our public health schools and medical school departments of public health can benefit tremendously from lectures, seminars and other presentations in which the biomedical, clinical, and epidemiological aspects of diseases and their possible causal factors are seriously discussed by knowledgeable faculty and trainees. This topic is fully discussed in Chapter 19.

CHAPTER NINE SUMMARY

GENITAL HERPESVIRUS INFECTIONS IN CLOISTERED NUNS AND THEIR SECULAR SISTERS

If genital herpesvirus is implicated in the etiology of cervical cancer, its frequency should be substantially lower in populations at low risk of this neoplasm than in populations at higher risk. Although their sexual practices have never been investigated, cloistered nuns are theoretically at low risk for cervical cancer in view of their lifelong habits of non-marriage and sexual abstinence.

Our long-term interest in evaluating the likelihood that the venereally transmitted HSV-2 virus is a significant risk factor in cervical cancer led us to design and undertake a study comparing the frequency of genital herpesvirus infections in Catholic nuns with that in their secular blood-related sisters. Confirming such a finding would constitute strong evidence of a causal relationship between this virus and the neoplasm. And, regardless of outcome, the successful completion of this investigation would demonstrate some of the unique capabilities of epidemiologic studies in studies of healthcare.

We completed lengthy negotiations with the School Sisters of Notre Dame and the Sisters of Mercy, two orders of 1,500 nuns in metropolitan Baltimore. A total of 500 nuns and 500 secular sisters under age 60 were selected, and all underwent

personal interview, medical record review, a self-administered vaginal irrigation smear, and a sampling of blood for herpesvirus antibody testing. It became clear to us that many of the nuns had not been as cloistered or protected from sexually transmitted diseases as was the case in earlier generations.

As this study was ending, a scandal with widespread political ramifications occurred when two nuns teaching at a Catholic high school in Baltimore were murdered. The Archdiocese and Baltimore Police Department became involved in a highly publicized, embarrassing, and long-lasting controversy, compelling us to close the study and refrain from publishing the findings. However, the lessons it taught, and its value to epidemiology and its practitioners, remain.

CHAPTER NINE

GENITAL HERPESVIRUS INFECTIONS IN CLOISTERED NUNS AND THEIR SECULAR SISTERS

BACKGROUND

If genital herpesvirus is implicated in the etiology of cervical cancer, its frequency should be relatively low in populations known to be at low risk of cervical cancer and relatively high in populations with higher risks of this disease. Cloistered nuns constitute a well-established low-risk group. The objective of this study was to compare the frequency of genital herpesvirus infection in nuns with that in their secular blood sisters. The incidence of cervical cancer among the latter should approximate that of the general population. By comparing religious sisters with their married siblings, one can learn a great deal about environmental factors in this disease, because the blood-relatedness of the two groups will make it possible to differentiate between hereditary and non-hereditary influences. If the study shows a significantly lower frequency of herpesvirus antibodies among the nuns as compared with their secular sisters, this will strengthen the hypothesis that genital herpesvirus is of etiological significance in cervical cancer.

DESIGN

Negotiations were completed for assembling two groups of cloistered nuns in the Baltimore area for participation in this study. Agreements were reached with the School Sisters of Notre Dame and with the Sisters of Mercy. The two orders consisted of approximately 1,500 nuns, of whom perhaps 800 to 900 were situated in the Baltimore Metropolitan Area.

About 85% of the nuns were under 60 years of age and agreeable to a personal interview. A complete listing of nuns in the two orders was prepared and the following information was collected: (1) For the nuns: name, address, date of birth, and race; and (2) For the female siblings: total number, number surviving, date of birth, lay/religious status, marital status, names and addresses of those surviving to the onset of the study. From this listing, study groups of nuns and secular sisters were selected in such a manner as (1) to provide a sufficient number of nuns below age 60 for statistical analysis (a minimum of 500) and (2) to minimize the extent of travel required to contact the nuns and their secular sisters. Only those nuns were included who had at least one surviving secular sister. The sister closest in age to the nun was chosen. If the listing indicated that the numbers were sufficient, two sisters were selected for each nun, whose ages straddle that of the nun herself. In this fashion, there were a minimum of 1,000 women in the study (500 nuns and 500 sisters) and a maximum of 1,500 (500 nuns and 1,000 sisters).

All selected nuns and secular sisters underwent a personal interview, review of medical records, self-administered vaginal irrigation smear, and sampling of blood for herpesvirus antibody testing. The questionnaire sought the following information: full name, date of birth, date entered

religious order, residential history, education, occupation, hospitalizations, operations, illnesses, and data on all siblings, living or deceased (including their name, birth date, address, live/dead status, marital status, hospitalizations, and illnesses).

Each respondent was asked to sign a consent form, which explained the purposes of the study procedures and which gave permission for the interview, record review, blood sampling, and vaginal smear. The discomfort associated with drawing of the blood samples was discussed, as well as the painless vaginal irrigation technique. The purpose and length of the interview was also mentioned, as was the respondent's privilege to request a pause, or even a halt, to any or all of the proceedings.

ANALYSIS

The analysis consisted primarily of comparisons between nuns and secular sisters in terms of the prevalence of herpesvirus antibodies, cervical atypias, and trichomoniasis. In addition, the sibling pairs or triplets were compared in terms of their medical histories and diseases. As this study was being completed, we congratulated ourselves on successfully organizing an inherently difficult study: We identified a population thought to be at significantly lower risk of a sexually transmitted disease and negotiated with them to permit a formal study. We obtained approvals from the superiors of the religious order, conducted personal interviews with the women on their personal lives including sexual experiences, and even obtained Pap smears by means of the Davis irrigation pipette. As we began to examine the results, it became clear that some of the nuns had not been as cloistered, or otherwise protected from sexually transmitted diseases, as one might have anticipated.

CONCLUSIONS

As this study was ending, a scandal with widespread political ramifications occurred when two nuns teaching at one of the Catholic high schools in Baltimore were murdered. The Archdiocese and the Baltimore Police Department became involved in a highly publicized, embarrassing, and long-lasting controversy, compelling us to close the study after its completion. These circumstances led us—at the behest of the Catholic order and a desire to avoid public controversy—not to take the final step of publishing the study results. The findings had suggested that sexual activity, as monitored by our measurement of HSV-2 infections, was more frequent than expected. But, instead of the cloistered sisters having a lower herpes antibody level than their married sisters, i.e. the confirming the study's hypothesis, the two groups had antibody levels that were similar, yielding a result that rejected our hypothesis in a very different fashion than anticipated. The lessons taught by this experience, and its value to epidemiology and public health, remains.

Our understanding of the herpes genitalis virus and venereal disease was broadened by this study and demonstrated the ability of clinical epidemiology to mount such studies, despite the delicate study conditions required. We hope that by opening the door to this arena, other investigators will carry on similar scientific missions, although this has not yet occurred. Rules and regulations governing human studies have multiplied logarithmically over the years since then, and classical epidemiological investigations of potentially significant factors in human disease are no longer being undertaken by the majority of professors and students in our medical and public health schools.

This study was unique among biomedical experiments of the time, in that it explored very personal factors in disease etiology without arousing much objection from the participants. It demonstrated that such studies could be conducted objectively and respectfully through clear-cut understandings between the religious orders, the subjects, their doctors, the investigators, and the university, and without excessive interference from state and federal government authorities. However, our final decision not to publish the findings—in order to avoid further embarrassment for the Catholic order of nuns—helped us avoid further entanglement in the legal consequences of this unanticipated study outcome.

CHAPTER TEN SUMMARY

THE MARYLAND CANCER REGISTRY: ITS DEVELOPMENT, UTILITY, AND POLITICAL DEMISE

Many countries around the world have cancer registries, enabling them to calculate cancer rates by age, sex, race, ethnic group, occupation, and exposure to environmental agents. Despite these noble objectives, all registries share two basic flaws. First, they are managed as governmental agencies, and their staffs are recruited and supervised as government employees rather than as members of an epidemiologically trained staff experienced in most aspects of health and disease. Second, as a consequence, registries are notoriously slow and incomplete in yielding patient data, and in producing useful analyses.

Another shortcoming of existing registries is their failure to track neoplasms as close as possible to the time of their diagnosis, when extraneous factors to be ruled out are minimal. Instead, the observer must usually deal with a mixed bag of early, late, and deceased cases, which unnecessarily complicates any analysis.

In the late 1970s, circumstances arose that enabled our Department to create a unique cancer registry for the state of Maryland. Its target population was the total population of Maryland, irrespective of where healthcare was provided or

death occurred. Data collection was the responsibility of the registry staff who visited all Maryland hospitals and selected others in neighboring states, on a regular basis. Diagnoses of patients identified from death certificates were validated whenever possible, and overall management of the registry was directed by members of our Department of Preventive Medicine faculty.

The Maryland Cancer Registry became fully operational within three years of its conception but, several years later, the Maryland legislature transferred the system to state control. The sudden death of the university's president was primarily responsible for the demise of this highly promising tool for studying and eventually controlling the distribution of cancer in a geographically defined region.

In writing this book on the future of public health, I resurrected and expanded my original recommendations for the registry. The proposal now is much broader than originally made in this chapter, as it now directly addresses the future of public health as a major branch of medicine. The reader is encouraged to read and consider the substance of Chapter 19, along with that of Chapter 10.

CHAPTER TEN

THE MARYLAND CANCER REGISTRY: ITS DEVELOPMENT, UTILITY, AND POLITICAL DEMISE

BACKGROUND

For nearly a century, countries, states, and eventually the World Health Organization have developed and maintained cancer registries. The aims of these rather expensive enterprises are to collect and document statistics on the prevalence and mortality of cancer, to compare rates of the disease among specific population groups, to assemble cases for epidemiological study, and to seek clues to the etiology and risk factors of specific neoplasms.

The Connecticut Tumor Registry, one of the earliest of such registries, has been in operation since 1935, serving as a member of the National Cancer Institute's SEER (surveillance, epidemiology, and end results) Program. It provides data on the incidence, follow-up, treatment, and survival of the cases in its database, and publishes impressive annual and supplementary reports on diverse aspects of cancer in Connecticut. The SEER Program as a whole produces data on cancer incidence and survival based on state, city, and other registries registered with them. The World Health Organization functions in similar fashion on a worldwide basis.

To the extent that a registry is actually population-based, much useful information can be derived therefrom. The distribution of cancer rates by type can be ascertained for age, sex, racial, and ethnic sectors of residents, as well as for geographic communities, specific occupations, and populations exposed and not exposed to specific environmental agents, and, at least theoretically, to evaluate cancer prevention programs. Cancer rates for groups treated in a specific hospital, or with a particular treatment regimen, may be compared to the total cases in the general population. A great many other useful functions could theoretically be served by population-based registries.

While the objectives of cancer registries are noble and potentially beneficial, none of them are presently designed to provide credible answers to most of the important health and disease issues that constantly arise. For example, if multiple cases of a particular cancer occur in a defined time period, might they be related to exposure to an environmental toxin? Or, if 10 cases occur in a community where only four were reported in the previous decade, what is responsible? Or, if a medical scientist develops an exciting new hypothesis on the pathogenesis of a specific neoplasm, can the registry provide him with a list of all patients in the registry who were diagnosed within the past year for possible inclusion in a clinical trial? Or, can the data be used to assess the long-term effects of HSV-2 screening, sputum specimens, fecal blood, or chest X-ray examinations on subsequent cancer risk?

Two basic flaws are present in all existing registries. **First, they operate as governmental agencies,** and their staffs are employees recruited, trained, and supervised as in most other public agencies, rather than as epidemiologically knowledgeable functionaries within a medical or public health school

environment. **Second, and partly as a consequence, they are extremely slow in maintaining up-to-date patient entry, validation, utilization, and completeness of the data**. On several occasions in the past, I have been informed that cancer data requested by me from a prominent state registry was late in being entered by several years, and therefore was unusable for my research purposes.

Many cancer patients in all registries are first reported at the time of their death, because state or national law requires a death certificate. Others come to the attention of the registry long after their initial diagnosis, which may occur years after the neoplasm was initiated. Perhaps minimal patients are entered into the cancer registry at or near the time of their original diagnosis. The admixture of these different categories of cancer patients wreaks havoc with studies aimed at eliminating a variety of noncausal correlates of the disease, before identifying the potential etiological factors.

The degree to which case mix in cancer affects the etiological conclusions varies with the natural history of the particular neoplasm. For example, a tumor manifesting shortly after exposure to the causal agent, and characterized by a quick lethal course, would be minimally affected by the relative slowness of its registration. At the other extreme, a tumor developing slowly, transitioning through premalignant stages such as dysplasia and in-situ lesions, and not becoming lethal until years later would yield markedly different estimates when sampled.

An underlying defect in all existing registries is their failure to track the neoplasms as closely as possible to the time of their diagnosis; therefore, the data analysis is almost always based on a mixture of cases in which the dates of disease onset or

diagnosis are highly variable. Thus, rather than tabulating information about cancers arising at about the same time, i.e. close to the initiation of the carcinogenic process when extraneous factors that must be ruled out as potential agents of disease are minimal, the opposite is the case: with every passing month or year since diagnosis, one is forced to consider greater numbers and varieties of potential causes (host-related factors such as age, immune status, occupations, other diseases, diet, travel exposures, etc.) that must be ruled out.

In the instance of cancers arising among residents living adjacent to a trash dump, for example, if the patients being studied were diagnosed over a 10-year time period, some cases might have arisen before the dump was even established, while others were exposed to its potential toxicity for variable periods of time. In studies of cancer risk by race, registries using prevalent rather than incident cases would be led astray if the region's resident population had experienced fluctuations in racial or ethnic composition over time.

In the late 1970s, circumstances arose which encouraged us to look into the possibility of creating a unique cancer registry for Baltimore City, which could eventually serve the entire State of Maryland. The registry was carefully designed to justify its relatively modest budget and came closer to fulfilling its research potential than any predecessor registry. A new president of the university had recently arrived, and Baltimore's popular and long-time mayor had just been elected governor. Cancer was again attracting public attention, with newspaper articles on rising cancer rates in certain neighborhoods that were thought by many to be due to environmental conditions.

I met with the newly appointed president and governor to discuss the importance of cancer control in Maryland, to share my personal experiences with the shortcomings of existing registries, and to solicit their cooperation in establishing a unique cancer-reporting system, the Maryland Cancer Registry, that would operate in a fashion different from that of all other registries, and yield benefits unattainable by any other. Rather than functioning as a state agency, it would operate as a division of the medical school, though its activities would be overseen by the Maryland Department of the Environment. Its staff would be recruited through the medical school and selected from candidates meeting the educational and experiential criteria for positions in the staff of the School's Public Health Department. Leadership would be selected from the senior epidemiological, biostatistical, and public health faculty and staff members. All administrative policies for the registry, including salary, benefits, promotions, and supervision, would be identical to those of the medical school, rather than the state government. In this fashion, it was hoped to reduce or eliminate the political susceptibilities of the registry, and emphasize its public health and research objectives.

Discussions led to legislative approval for the establishment of the cancer registry and for a competitive process to select the winning academic bidder. Our Department of Preventive Medicine, the ultimate winner, then initiated a three-year process of developing the cancer registration system, assembling and training the staff, and perfecting a computer system to operate the registry and manage the analytical and management aspects of the effort. We were fortunate in having our own cadre of computer- and data-processing personnel already working in the department's Health Data Management Center (HDMC), ready and eager to assume

responsibility for developing this large-scale clinical information system. The department was united in its enthusiasm for undertaking the largest and most elaborate research development in its history.

DESIGN

The Maryland Cancer Registry was uniquely designed, completely different from all others registries in its structure, functions, and utility.

1. **The target of the registry is the total population of Maryland** that is diagnosed with cancer, irrespective of where diagnosis or treatment is sought. All patients will be followed, including those who leave the state for any reason, until death occurs.
2. **Patient identification and data collection will be obtained entirely by the registry staff**, who will visit all hospitals in Maryland and selected hospitals in Delaware, Pennsylvania, Virginia, and the District of Columbia, on a regular basis, timed according to the registry's estimates of requisite frequency.
3. **Patients identified from death certificates, published obituaries, newspapers, relatives, and all other sources beyond hospital records will be validated** by confirming their authenticity through abstracting their hospital records and communicating with their physicians, whether in Maryland or beyond.
4. **Within each hospital, patient records will be abstracted from the record rooms, pathology departments, and other sources** selected by experienced senior staff of the registry.
5. **The HDMC of the Department of Preventive Medicine will develop, test, and certify for use the**

computer system designed for the registry. The system will record the abstracted data of all cancer patients after each hospital and clinic visit; encode the information for entry into the computer system; validate the data entered; correct all identified errors; and generate all required reports.

6. It is anticipated that **advances in computer technology now underway will soon make it possible for registry staff to enter patient data directly into laptop computers and automatically transmit the data to the registry** mainframe in the medical school. This will substantially accelerate, and perhaps reduce the cost of, the data collection process.
7. **The initial patient target will include all patients within one month of their entry into a hospital system as cancer patients.**
8. **Over time, other patient data sources will be explored as to their feasibility for augmenting the hospital-based data sources.**
9. **The registry will enable cancer-related studies to be undertaken in a fashion that is essentially impossible at present**, given the usual slow reporting and bureaucratic-type registries that now exist. Examples of possible studies would include: (a) estimating the extent to which a community dump or toxin-producing factory produces specific cancers in a neighborhood; (b) determining the extent to which a newly instituted program of sputum examination, HPV screening, fecal blood examination, or chest X-rays reduces a particular type of cancer in a given neighborhood; and (c) determining whether recent population in-migration or out-migration has had a demonstrable effect on reported cancer incidence.

10. Another distinguishing feature of the new Maryland Registry system is that, **in the future, other major diseases can be added to the roster of patients being identified and followed**. Extensive discussions were held with leaders of major Maryland psychiatric institutes about the possibility of adding psychiatric diseases to the registry system. Coronary heart disease, stroke, certain genetic diseases, and a variety of other conditions, including viral and other infectious diseases, could be added in similar fashion. All such program elements could be achieved at far lower cost than depending upon other slow and incomplete registries.

As the development of the Maryland Cancer Registry proceeded, the unique advantages of this revolutionary system became increasingly evident. Members of our academic faculty with an interest in the pathogenesis and control of cancer will have an influential voice in operating the system and helping to create a favorable environment for its future success. Other registries, being state or federal agencies established by and accountable to political bodies for their structure, staffing, funding, and management, remain permanently at risk of political interference. It seemed manifestly clear to me that a cancer registry created by an experienced medical school department like ours, with its long history of clinical research and teaching in the cancer arena, was likelier to succeed over the long run than those developed by governmental or political bodies.

A few other significant features of the Maryland Cancer Registry are the following:

1. This unique area-wide cancer registration system will **permit the documentation of each case of cancer**

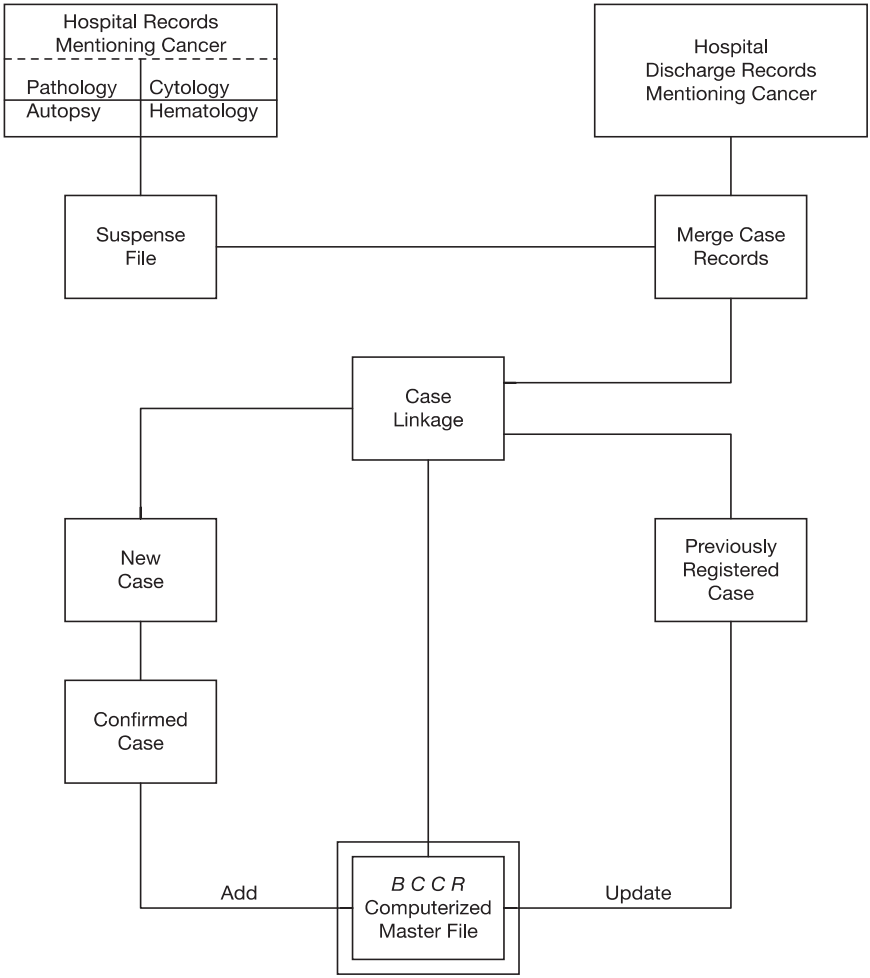
diagnosed in the state, by age, sex, race, and a number of other familial, behavioral, environmental, and other variables within a few days of their diagnosis.

2. The **rapid reporting of cancer cases to the registry will make possible an array of cancer-control activities that are presently beyond the capability of all other registries.** For example, alerting the public to potentially hazardous sites of cancer development, or permitting researchers to quickly assemble cancer cases of particular types for new studies or treatment trials.
3. **Development of the registry in all its aspects will be led by experienced faculty members of our Department of Public Health who are knowledgeable in all aspects of the project**: epidemiology, biostatistics, computer science, data collection, analysis, and personnel management, as well as in cancer research and patient care.
4. **The registry could readily become a major asset to the state in cancer-control programs, as well as other disease-related programs, if they are added to the system**, as we have suggested above.
5. **The registry can also generate reports of utility to each participating hospital in respect to their cancer patients, and later, to other registered diseases of concern.**

ANALYSIS

The original table of organization of the registry and an outline of information flow at the time of its original design as the Baltimore City Cancer Registry are shown in the flowchart below. As it eventually evolved as a statewide system, a number of administrative and organizational modifications were

Baltimore City Cancer Registry Information Flow Chart



required, and the computer capabilities for large-scale data processing and analysis were greatly increased. But the basic structure of the original proposal, with its policies and management under the medical school's Department of

Preventive Medicine, and its rapid-reporting features, remained unchanged.

DISCUSSION

The lengthy process of bringing the registry to fruition was intensive and complicated, in part because it was carried out by an academic consortium lacking the political and legal resources that are usually available to state and federal governmental agencies or private companies. Adding to the complexity of the project were innumerable meetings of the senior staff with Maryland state government officials, hospital directors, leading physicians, and members of the general public to discuss the merits of the proposal, provide general information, resolve issues, allay apprehensions, and bolster support for the enterprise. Many meetings with senior members of the HDMC of the Department of Preventive Medicine were also held to discuss, debate, and finalize the types and manner of data to be collected. In addition, field trials by registry staff members to test the proposed data forms in participating hospitals, and to assess the optimal frequency of hospital visitation for data abstraction, were also necessary.

All of these issues required several years to complete. At the conclusion of the planning and practice phases, all requisite forms were designed and tested, and the data collection staff were recruited, trained, and starting to collect and process the patient data. By that time, it became clear that the rapid-reporting system was, in fact, working as planned. The Maryland Cancer Registry became fully functional as the nation’s first rapid-reporting cancer registration system. Its future seemed assured with secure funding and a newly appointed university president who was highly supportive.

But, suddenly and unexpectedly, the university president suddenly passed away and a new governor with another political view quickly asserted control over the registry. Its management was transferred away from the medical school to the state government, and the operating system quickly regressed to the level of all the other slow-reporting registries in this country and abroad. The medical school's epidemiology staff and its HDMC were relieved of their responsibilities, and the Maryland Department of Health and Mental Hygiene has been operating the registry in the usual dysfunctional manner since then.

This outcome, though shocking, did not surprise me. Shortly after our proposal to the state was approved, it occurred to me, a political novice, that after the registry became fully functional, a critical period would arrive when its unique advantages over existing registries would become apparent. It would then become a tangible political asset in the state, and pressure to move it from the jurisdiction of the university to the state government would greatly increase. I discussed this potential threat at the highest level with the university and medical school leadership on several occasions, but was unable to convince them that the registry was sufficiently important to merit strong defensive measures on the university's part. Within several years of it becoming a full-time statewide system, the registry's authority was transferred from the university, all operations were moved to a state office building, and, from that moment on, it has been managed by government employees. And, as we expected, the Maryland Cancer Registry quickly reverted to the traditional format established by the SEER Program of the federal government. Its unique advantages of rapid reporting and full patient participation, and central role as a vigorous academically

based cancer control research and management entity, were all abandoned and are now nearly forgotten.

I reiterate here that our successful establishment of the registry in a medical school setting, despite its eventual political demise, would not have been possible at all in other biomedical institutions lacking the teamwork, spirit, and intellectual, clinical, and research resources of our Department of Preventive Medicine. Its cadre of medically trained epidemiologists, associated clinicians from our and other medical school departments, biostatisticians with extensive experience in medical research, computer technologists skilled in managing population-level data sets, teams of experienced interviewers, and other critically essential staff members were the basis for its unusual, but limited, success. In other words, the years spent in building this department's unique faculty and staff, developing its computer resources, and interacting meaningfully with the clinical and basic science departments over decades of time, were the ultimate key to this remarkable achievement. We hope that a permanent disease registry of this type can be instituted by another far-sighted group, which is able to offer more powerful resistance to government control.

ADDENDUM

Since writing Chapter 10, I have spent substantial time considering the future prospects of public health, and my conclusions are summarized in Chapter 19. The reader will notice that I recommend expanding the role of the cancer registry to become the department's multifunctional Health Statistics Center. In this role, it would accept fee-based contracts to prepare required health and disease reports for hospitals and government agencies, and assume the important

role of providing objective science-based data to the nation during pandemics and other health emergencies. Such activities would yield substantial funds for the newly conceived Clinical Public Health Department and would provide a potpourri of meaningful ancillary experiences of relevance to the students and faculty.

CHAPTER ELEVEN SUMMARY

MEDICAL INFORMATICS TRAINING IN THE HEALTH SCIENCES

After the sudden death of Dr. T. Albert Farmer in 1984, and with the gradual recovery from his absence and strong support, the department turned its attention to a paradoxical problem: the absence of academic programs to train medical students and biomedical researchers in computer applications at a time when this technology was revolutionizing healthcare. In our view, continuing such developments in the near absence of major input from the medical profession would create serious problems for medicine and biomedical research.

The dearth of medical professionals in the leadership of developing computer software and biomedical applications has already reduced the influence of biomedical reasoning in guiding the process. Computer engineers usually lack knowledge and experience in biomedicine, and their products tend to be less than optimal for clinicians and health researchers who will be among the ultimate users of this technology.

Our first step was to establish a Health Data Management Center (HDMC), a computer-based resource for data entry, programming, systems design, computer graphics, statistical analysis, and related information management services. Staffed by biostatisticians, computer scientists, programmers, and data entry clerks, the HDMC grew to become a major

resource on campus to meet the programming and data management needs of faculty and student researchers in the medical school. The funding mechanism was unusual: it was supported by data-processing monies received by the faculty in their research awards, a provision approved by the faculty after understandable opposition from a minority of them.

The benefits of this basic informatics system were many, including:

1. The department became far less dependent on the medical school for funds.
2. The department became more competitive in seeking research funding.
3. All faculty and students had access to computer services, whether they had funds or not.
4. HDMC staff positions, no longer linked to funded grants, became more secure for the employees. Long-term appointments became feasible.
5. At this early stage of the computer age, the department's self-funding computer budget made possible the rapid development of the Maryland Cancer Registry, through recruiting new staff members with advanced computer skills (Chapter 10). It also benefited our comparative study of dermatologists and family physicians (Chapter 13).

The next step was the department beginning to develop a two-tiered medical informatics program for dual categories of postdoctoral students:

a) Students with previously earned doctorates in engineering, physics, computer science, or applied mathematics would enroll in the **Biomedical Systems**

Track to prepare for careers in computer-related teaching and medical research in public health.

b) Physicians, dentists, and nurses would enroll in the **Health Information Systems Track** of the program to pursue careers at the highest level in computer science and human health.

The following courses would inaugurate the program:

1. PREV 650: Health Systems Analysis I
2. PREV 651: Health Systems Analysis II
3. PREV 652: Theory of Data Structures and Data Models
4. PREV 653: Information Management
5. PREV 654: Biomedical Systems Methodology
6. PREV 655: Computer-Aided Analysis
7. PREV 656: Biomedical Modeling and Simulation
8. PREV 657: Biomedical Decision Making

CHAPTER ELEVEN

MEDICAL INFORMATICS TRAINING IN THE HEALTH SCIENCES

BACKGROUND

The sudden death of Dr. T. Albert Farmer, the university president, and the unexpected termination of his remarkable support for our department compelled us to turn our attention to a number of critical problems in need of resolution. Perhaps the most significant was the paradoxical situation of computers revolutionizing healthcare technology in the absence of academic programs to train medical students and biomedical researchers in this new technology. Our view was that, if the technological developments continue in the near absence of major input from the medical profession, serious problems for medicine and biomedical research would arise.

The dearth of medical professionals in the leadership of developing computer software and biomedical applications has already reduced the influence of biomedical reasoning in guiding the process. Computer engineers in charge of technical developments usually lack knowledge and experience in biomedicine, and their products tend to be less than optimal for clinicians and health researchers who will be among the ultimate users of this technology.

I experienced some of these problems during my own graduate school years. At that time, biomedical students had

to write their own analytical programs in an appropriate computer language for their theses and other research assignments. The computer often sent procedural and error messages that were clearly not designed to be understood by physicians or other non-computerniks. This led me to ask why the system being created seemed to be tailor-made for the technicians rather than the biomedical users. I was eventually led to the conclusion that programs to train the new generations of healthcare professionals in computer technology should make a serious attempt to increase their influence on future developments in computer applications for healthcare and biomedical research.

Our first action in this arena was to establish the department's Health Data Management Center (HDMC), a computer-based resource for data entry, programming, systems design, computer graphics, statistical analysis, and related information management services. Staffed by biostatisticians, computer scientists, programmers, data entry clerks, and other technicians, the HDMC grew to become a major resource on campus designed to meet the programming and data management needs of faculty members and student researchers in the medical and other health professional schools.

The funding mechanism for supporting the HDMC was a bit unusual in academia at that time. Instead of depending on university funds, it was supported primarily by data-processing funds received by departmental faculty who had been awarded governmental or private grants for their research. The department faculty approved this provision after understandable opposition and discussion. The benefits of this developmental system were many, including the following:

1. **The department became far less dependent on the medical school for data-processing and computer-development funds.** It also found itself regularly solicited for advice about computer-related developments by the school administration itself.
2. **The department became somewhat more competitive in seeking research funding**, as our computer costs could be reduced.
3. **Departmental faculty, staff, and students had access to all computer services of the HDMC, whether they were funded or not**. Other impediments to students' learning or applications involving computer technology were substantially reduced.
4. **HDMC staff positions were no longer linked to funded grants or University budgets, so that staff appointments could be far more secure for the employees over the long term.** New appointments to the HDMC were more easily made, and long-term appointments became feasible. With the HDMC growing in this fashion, promotions and new job opportunities increased within the department. In those days, many computer specialties were largely self-taught, and the HDMC went out of its way to encourage all staff members to expand their arenas of expertise.
5. **An academic department developing substantial computer-related capabilities for biomedicine at this early period of the computer age would not have been possible had we depended on university funding**. The Maryland Cancer Registry, for example, relied heavily on recruiting new staff members with basic or more advanced computing skills who could rapidly learn to undertake important roles in such a complex project. Our comparative study of the cost of treating disease by dermatology versus family medicine

> faculty required computerniks with the skills to rapidly develop an automated clinical information system. These projects motivated us to set in motion the beginnings of the department's medical informatics training program.

A necessary step in the evolution of our medical informatics training program was taken when I, as a Board member of the Governor's Council on Toxic Substances, recommended that the Maryland Department of Health & Mental Hygiene develop a computerized health information resource encompassing a statewide cancer registry, a toxic substances registry, a birth defects registry, and an occupational disease reporting system. Such a resource could collect information on cancer, birth defects, toxic substances, and occupational diseases, and enable the state to better protect the public against toxic exposures, cancer, and birth defects, while systematically searching for clues to the pathogenesis of these hazards to human health. This recommendation was entered into the public record and our first success in the venture occurred when the department won a competitive state contract to develop and operate the Maryland Cancer Registry. Our principle competition in this contest came from our neighbor, the highly regarded Johns Hopkins medical institutions.

At a later date, the University of Maryland Hospital requested that our HDMC begin to upgrade the hospital's largely manual information system for its cancer patients. It also asked for our suggestions to help the hospital control costs, assure the quality of patient care, improve the federally mandated diagnosis-related groups (DRG) patient classification system, and eventually conduct a marketing survey.

It has already been mentioned that developing an academic program in healthcare informatics was especially difficult because of the rarity of senior-level faculty with dual expertise in advanced computer science and medicine. In the 1980s, computer scientists were situated primarily in high-tech corporations or in university departments such as electrical engineering. For most of such individuals, their training and research interests were remote from public health. The medical school had a small number of faculty members with dual backgrounds, but they were already pursuing their own interests beyond public health, they had attracted few associated students or fellows, and offered few, if any, academic courses. Without exception, they also lacked training or interest in classical epidemiology or clinical medicine.

We invited a few electrical engineers to enroll in our basic epidemiology course, but they showed little interest in the subject or with the medical students whom we hoped might help them acquire a deeper understanding of basic epidemiological principles. After several years, we succeeded in identifying a small number of faculty members engaged in higher-level computer-rated studies, ranging from signal detection and analysis, physiological research, biomedical engineering applications in trauma, and imaging and mathematical modeling in radiation oncology, as well as in pharmacokinetic studies.

Officials in the several health professional schools on campus, and some individual faculty members, then began to call for inaugurating computer-related programs designed for faculty and health professional students interested in applying advanced computer technology to the health and disease arena. They spoke in favor of enlarging the relatively limited

computing facilities of the medical school and providing easier access to the Departments of Electrical Engineering and Computer Science at the College Park campus some 30 miles away.

It was at that point that we decided to begin developing a two-tiered medical informatics program, by establishing a mentor-based research program for two categories of postdoctoral students. The first group would be those with previously earned doctoral degrees in engineering, physics, computer science, or applied mathematics, for which a relatively high level of computer knowledge had already been achieved. The second group would consist of physicians, pharmacists, dentists, nurses and other doctoral-level health professionals with documented quantitative skills but a more elementary background in basic computing.

The postdoctoral students from the first group would matriculate into the **biomedical systems track** of the program. The program would augment their strong quantitative and computer skills with courses, seminars, and research projects in the basic medical sciences, in order to prepare for careers in computer-related teaching and research in medicine and public health. The coursework would emphasize signal analysis, image processing, simulation, decision methodology, and computerization of laboratory and clinical data. Candidates from the second group would matriculate into the **health information systems track** of the program. Their academic goal would be to acquire new skills in computer science and epidemiological aspects of public health, in order to pursue careers requiring a higher order of capabilities in both computer science and health science. The courses would deal with the design and management of large information

systems, database technology, systems design, and related computer-related subjects.

A few examples of the types of students we had in mind may be cited here.

1. An **electrical engineer or computer scientist** desiring to pursue a career in which his computer capabilities are applied to problems in biomedicine. He has already mastered the computing skills, but lacks knowledge and experience in the biomedical sciences, epidemiological reasoning, design of human studies, and healthcare systems. We would enroll him in the biomedical systems track of the medical informatics program to acquire fundamental knowledge about human health and disease, and engage with his mentor on designing a project of interest.
2. Another type of student would be a **physician** or nurse, already competent in medicine, seeking an academic career involving computer science applications. For example, she might wish to develop clinical information systems at a hospital, industry, or medical school to permit classification of diseases by severity of illness, presence of risk factors, and genetic relationships. Such a student would enroll in the health information systems track of the master's degree and acquire the epidemiological, biostatistical, and computer skills to meet the needs of her chosen career.
3. A third example would be the **graduate of a school of library science** who aims at a career in an academic health sciences library and realizes the importance of computer science in the future development of such institutions. Such an individual would enroll in the health information systems track and concentrate on

courses in epidemiology, biostatistics, and computer science applications.

The medical informatics trainees would devote substantial time to **biomedical research projects** involving computer technology, in association with faculty mentors engaged in investigations pertinent to the trainees' interests. All trainees would also be required to participate actively in seminars, journal clubs, and workshops specially developed for the program, and scheduled throughout the academic year.

Seminar speakers in the program would include well-established experts in medical informatics and computer science who are involved in health and disease research at the University of Maryland and other major academic institutions. Our proximity to a wide variety of university and governmental institutions in the Baltimore/Washington DC corridor would facilitate the recruitment of excellent seminar presenters. Our past experience in scheduling well-attended seminars demonstrates the feasibility of this approach.

Informatics journal club meetings would be held on a regular basis throughout the year, led by the trainees themselves with the support of faculty mentors. The experience gained by the trainees in preparing their own journal club presentations and those of their classmates would broaden their biomedical perspectives, a process which would be especially important in a newly developing field such as medical informatics.

Regularly scheduled **medical informatics workshops** would be designed for the trainees to present their research projects to fellow students and faculty mentors. These would be required at the initiation of each project, when the emphasis

would be on the background, purpose, and methods of the research, as well as at the completion of the project, when the emphasis would be on the findings and conclusions. This model of presentation also is derived from the department's experience, when workshops for postdoctoral trainees proved to be quite successful.

The regularly scheduled seminars, journal clubs, and workshops attended by the informatics trainees will serve several important functions. They will create an "ethos" among the participants, i.e. a sense of belonging to a larger community of medical informatics specialists at the medical center. The trainees and their faculty mentors would become increasingly familiar with each other and their shared research interests. This experience would benefit the trainees in creating a hospitable medical informatics environment on campus, as well as in helping the students learn about resources and colleagues of potential utility for their own projects in health and disease.

A further benefit of the informal academic training components described above is that the diverse aspects of medical informatics would become increasingly familiar to the trainees and the faculty as they participate in the seminars, journal clubs, and workshops dealing with the biomedical arenas in which informatics plays important roles. These experiences will broaden and deepen each fellow's understanding of the arenas in which they are being trained. Pedagogically, this will resemble the situation with epidemiology, another relatively isolated biomedical field, which has applications to most of biomedicine, from basic science to clinical medicine and beyond.

In the first few years of its existence, the following eight academic courses will be offered to the postdoctoral and predoctoral trainees in health informatics:

1. **PREV 650: Health Systems Analysis I.** Methods for representing information flow, data structures, and the development of input and output formats for health systems. Actual examples of applications in the health arena will be utilized. A companion laboratory session emphasizing hands-on experience will be scheduled to follow each lecture.
2. **PREV 651: Health Systems Analysis II.** Emphasis on planning, organizing, and managing health systems, including the theory and practice of structured analysis as a method of modeling health systems. A companion laboratory session emphasizing hands-on experience will be scheduled to follow each lecture.
3. **PREV 652: Theory of Data Structures and Data Models.** Selection and procurement of database systems will be discussed and practicum experience in the design, development, and administration of health-related databases will be offered. A companion laboratory session emphasizing hands-on experience will be scheduled to follow each lecture.
4. **PREV 653: Information Management.** This course, dealing with hardware and software components of healthcare systems, will focus on relationships between hardware architecture and systems software, networking, data storage, and distributed systems as they relate to the development of healthcare systems. A companion laboratory session emphasizing hands-on experience will be scheduled to follow each lecture.

5. **PREV 654: Biomedical Systems Methodology.** Conceptual foundations and basic analytical and computer-related skills required for more advanced medical informatics courses. Topics include mathematical characterization of elementary signals; linear and nonlinear systems; architectures of analog and digital systems; state-space and algorithmic concepts; graph-theoretic methods; machine representations and computer structures; algorithm design and machine implementations; software tools; computer-aided time-domain and frequency-domain analyses; and interactive information processing. Companion laboratory sessions emphasizing hands-on experience will be scheduled to follow some lectures.
6. **PREV 655: Computer-Aided Analysis.** Fundamentals of biomedical signal and data processing of relevance to clinical medicine and basic science research. Topics include principles and algorithms for data acquisition and display, filtering, and feature extraction. Emphasis on commercially available computer-based tools. Applications include physiological monitoring, simulations, examples from clinical and laboratory medicine, and ongoing biomedical research problems. Companion laboratory sessions emphasizing hands-on experience will be scheduled to follow some lectures.
7. **PREV 656: Biomedical Modeling and Simulation.** Intensive introduction to biomedical problem-solving by means of algorithmic techniques and computer simulations. Topics include modeling, parameter identifiability, estimation, least squares, maximum likelihood, model validation, statistical hypothesis testing, bad data anomaly detection, and robust estimation. In-depth discussion of available software packages. Companion laboratory sessions emphasizing

hands-on experience will be scheduled to follow some lectures.

8. **PREV 657: Biomedical Decision Making.** Intensive introduction to the use of numerical and symbolic methods for decision making in medical practice and research. Introduction to strengths and limitations of current technology. Topics include: linear and nonlinear programming; decision analysis; sequential decision-making; Markov models; reasoning and representation; artificial intelligence ideas and techniques; expert system implementation; and discussion of available software. Companion laboratory sessions emphasizing hands-on experience will be scheduled to follow some lectures.

Postdoctoral students in both medical informatics tracks will initially enroll in a one-year program without a degree being offered. However, should some wish to extend their program by another year, a master of medical informatics degree would be awarded. The additional time would be devoted to a serious research project and to additional coursework in the department. The department recommends a minimum of one year in medical informatics training for all postdoctoral trainees, although shorter exposures may be permitted.

The trainees will not have any responsibilities or unsupervised access to human patients. However, those working in clinical environments (e.g. the Shock Trauma Center, neurology, obstetrics and gynecology, etc.) will be able to access patients through their faculty mentors. It is also anticipated that trainees' access to patients will be required in projects involving the monitoring of human functions in specific disease situations. Students entering the informatics program will be subject to the academic regulations of the Graduate

School, as well as the Department of Preventive Medicine. In addition, trainees may also enroll in graduate-level courses offered by any of the basic science departments in the School of Medicine, or any other division of the University of Maryland.

The research project of each trainee will be a major responsibility of the assigned faculty mentor based in an academic department at UMAB. It will be the responsibility of the program director of informatics research training and the Informatics Advisory Committee to periodically evaluate each trainee's research project to assure maximum educational benefit and to undertake whatever action is necessary to assure the maintenance of a high-quality mentor–trainee relationship.

A designated faculty member will serve as the principal advisor for each trainee. In addition, a three-member Trainee Research Subcommittee will be appointed for each trainee, with the mentor serving as chairman. The other two members will be selected to best meet the unique educational and research needs of the trainee. In some cases, one of the latter will be a member of the Advisory Committee on Computer and Information Science and Engineering (CISE) based in the College Park campus of the university. Our department's director of informatics research training and his designees will meet with the trainees and mentors on a regular basis to assure the highest possible quality of informatics research and education for each student. Degree candidates will adhere to all pertinent university and departmental regulations on degree candidacy.

Because faculty members of the Department of Preventive Medicine are experienced in evaluation techniques, the

monitoring and assessment of the trainees and their programs should not be difficult. Methods similar to those developed to evaluate the existing academic programs will be applied to the medical informatics program. These will assess information from the mentor, the Trainee Research Subcommittee, the Informatics Advisory Committee, course instructors, and seminar leaders, as well as the students themselves. Assessment of long-term outcomes, such as ultimate career choices and their degree of success, outcomes of trainee recruitment efforts, performance of participating faculty, and recruitment of new informatics faculty, etc. will all be routinely evaluated.

An additional advantage of basing the informatics program in the Department of Public Health of the medical school is the fact that so many computer-related activities are already centered there. Examples include the HDMC, which serves the statistical needs of many medical school faculty and students, the Maryland Cancer Registry, and the Survey Research & Development Center.

The Medical Informatics Research Training Program grew steadily for several years but did not survive my decision to resign as department chairman. A major complication was that my successor succumbed to pressure from faculty members who wished to rescind their agreement to share their data-processing funds with the HDMC. This resurrected the traditional divide of faculty and students into those with and those without funds for their analytical needs. An important lesson to be learned from this effort is that new ideas in academia are hard to achieve and sometimes even harder to sustain.

A moderately larger version of our HDMC at the University of Maryland could serve as a model for public health schools and medical school departments of public health to emulate in developing medical informatics training programs. Two types of students should be sought: (1) **Individuals skilled in information technology, who are interested in producing useful computer-based health and disease applications**; and (2) **Physicians, nurses and bioresearchers without strong computer skills, interested in enhancing their computer-based research capabilities.**

CHAPTER TWELVE SUMMARY

EPIDEMIOLOGIC ASSESSMENT OF THE COVID-19 PANDEMIC

The COVID-19 pandemic of 2020 began in January, 2020 when a bat virus was isolated from a woman in Wuhan, China, who had eaten at a wet food market, or possibly escaped from a nearby virology laboratory. The infection has probably killed thousands of Chinese in Wuhan, while also infecting millions of others worldwide who were largely resistant to the illness or immune to it. The Chinese government allowed millions of travelers to fly from Wuhan during the incubation period of the virus, resulting in a worldwide pandemic. Neither governments nor medical authorities were initially able to formulate policies to address the emergency. There was no effective vaccine, no clinical treatment, no diagnostic test, and no serologic test for its antibodies.

To confront this dilemma, the President of the United States met daily with his advisers and the directors of the federal health agencies, and addressed the general public frequently. He offered the kind of advice that one would expect from a political figure with a strong business background but who lacked meaningful experience with major health and disease issues. Unable to discuss the pathogenesis of the outbreak, he emphasized his ability to expedite delivery of initially unavailable face masks, gloves, ventilators, and other supplies requested by the states, and poured money into rapidly

developing diagnostic and screening tests, while echoing the medical views of his advisers and the Center for Disease Control. His media appearances were not particularly effective in calming the public concern.

The CDC and medical advisers issued almost daily statistical reports, which were essentially useless in helping the public understand the pandemic. No systematic data was provided on the age, sex, or racial distribution of the patients, or their specific disease manifestations. For example, had the age distribution of cases been clearly disclosed, the public would have immediately understood that the prime target of the pandemic was the elderly population, and New York could have prevented the multiple deaths following the mandatory transfer of such patients to the state's nursing and convalescent homes. If the paucity of cases occurring among young children had been recognized, the nationwide closure of schools might well have been avoided, to the great relief of the public at large.

To avoid such terrible problems in the future, we recommend the greater utilization of the clinical talents and expertise within the academic community in our medical and public health schools. A prime goal should be upgrading and relying upon the genuine experts on pandemics, those in full-time teaching and research positions in medical academia, rather than limiting them to comments on decisions already made by presidential advisers and government health agencies. A mechanism for achieving this, by establishing a few Clinical Public Health Departments and Health Statistics Centers in a limited number of medical and public health schools, is described in this chapter.

CHAPTER TWELVE

EPIDEMIOLOGIC ASSESSMENT OF THE COVID-19 PANDEMIC

BACKGROUND

The pandemic of a corona virus began in January, 2020, since it was isolated from a woman in Wuhan, a province of Hubei, China, who had eaten bat-infected food at a wet food market, or possibly from a nearby virology research laboratory where bat viruses were being investigated. The infection probably killed untold thousands of Chinese in Wuhan, while also infecting multiples of their contacts that were found to be largely resistant to the illness or immune to it.

As a result of lax or unenforced regulations, China permitted several million people in Wuhan, both Chinese and foreigners, to fly to multiple locations worldwide throughout the incubation period of the epidemic without restraint. The inevitable consequence was that a serious epidemic in China quickly became pandemic in many regions of the world.

Neither governments nor medical experts were initially capable of formulating policies to effectively deal with this emergency. There was no effective vaccine to immunize the population, no specific treatment for the disease, no diagnostic test to identify infected patients, no serologic test for its antibodies or proof of previous infection, and,

therefore, no straightforward way to assess the spread of the pandemic or its eventual decline.

Faced with this dilemma, the President of the United States met daily with his advisers and the leaders of powerful federal health agencies such as the Centers for Disease Control (CDC), the United States Public Health Service and the National Institutes of Health. He made frequent public appearances, during which the crisis was discussed with the general public. What he offered is what one would expect from a political figure with a strong business background who lacked meaningful experience with major health and disease issues. Unable to discuss the pathogenesis of the outbreak, he emphasized his ability to expedite delivery of initially unavailable facemasks, gloves, and ventilators to patients, and largely echoed the views of his medical experts and the CDC. His media appearances were marginally effective in calming the public concern.

Epidemiology has no role to play in providing the physicians, hospital beds, isolation procedures, ventilators, face masks, surgical gowns, and other material goods needed during an epidemic. As for diagnosing the viral infection, epidemiologists can participate with the basic scientists in developing and validating the actual tests. But, for interpreting the statistics on the progress or decline of the epidemic, the death rates, and the specific populations at high risk, the views of the clinically experienced epidemiologists should be of prime concern. At present, this role is played by Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases and Dr. Deborah Birx, Coordinator of the Coronavirus Task Force. In their presentations, the latter appear more concerned with potential aftereffects, such as a possible second wave of the epidemic, than the urgent need to

return the population to school, work, and social normalcy. They seem more determined to emphasize hypothetical worst cases, than commenting on the extremely low mortality rates of COVID-19 nationally.

Clinically active physicians are now beginning to advocate a more rapid reopening of society, along with a concentration of medical attention on the highly susceptible elderly population. The miniscule proportion of children developing a variant of the pandemic with fever, lymphoid edema, and other symptoms must also be investigated, but no one can now deny that mortality from COVID-19 occurs primarily in elderly patients with major disease burdens.

Since the pandemic began, the President's health agency leaders have appeared daily on television to describe the government's efforts and issue progress reports. They regularly report on two statistics at each appearance: "Total Deaths from COVID" and "Confirmed Deaths from COVID" in the United States, in selected states, and across the world. Each of these statistics, as offered, is almost completely useless. If only one additional statistic had been offered, viz. age of patient, a basic characteristic of the virus would have been immediately identified and defensive actions could have been taken. We now know that the pandemic primarily kills the elderly, a fact that should have been used to prevent the transfer of elderly patients into nursing and retirement homes where the death rate is maximal. But the governor of New York is still denying his responsibility in this matter.

Another basic statistic that was revealed after undue delay is that youngsters and school-age children are overwhelmingly immune or highly resistant to COVID infection. Had this information been publicly known, the cancellation of school

and university classes for a year would not have occurred, along with its dire economic and social ramifications. Even physicians and nurses lacking elementary epidemiological training should have realized that an early step in organizing a medical plan is ascertaining the age, sex, and race of the patients and their mortality rates. Yet no such chart has yet been offered at most public meetings.

Estimates of the cost of the pandemic in the United States to date far exceed several trillion dollars, with no end in sight. It is immensely important that the nation prepares itself to deal with any future health emergency of such magnitude. One novel step in this regard may now be taken into consideration, if political considerations can be held in check, viz. the institution of a legally mandated role of academic medicine in dealing with such crises. At present, the President and his advisers play a central role, and it is unlikely that any future Chief Executive will have relevant training or experience in major health issue management. The NIH, CDC, and other federal health agencies will necessarily be heavily involved, as they are in the present COVID matter, but they are unlikely to provide creative solutions beyond the predictable and very slow government-type remedies.

Academic medicine, for all its diversity and shortcomings, is the nation's untapped reservoir for the most clinically informed sector of society which, until now, has played little part in systematically advising the government on scientifically viable solutions to its problems of health and disease. The failure of the government to inform the public of the age distribution of COVID deaths and the patient immune status could not possibly have occurred if an experienced academic physician with basic clinical training were presenting the statistics. Nor would the race, sex, and presence of other

serious diseases be omitted from the daily reports. How different would the public's reaction to the epidemic be if it were known that the elderly are the prime target of the virus, children are rarely affected, and data are unavailable for working-age adults! The effect of the elderly population's co-morbidities such as heart disease, pulmonary disease, neoplasia, et al. on their response to COVID-19 is additional clinical data that must always be considered.

Statistics on the pandemic in general have not been generated systematically as they arrive haphazardly or randomly from various regions of the country. Physicians are submitting death certificates that do not clearly distinguish between patients dying of a COVID-19 infection and those dying of a well-established other disease together with the viral infection. The government is promoting a vaccine, which it asserts could terminate the infection, but there is no assurance that it will be available by next summer, or that it will be effective. Developments on new diagnostic tests are also underway, but their merit and availability remain questionable.

The health agencies, led by Dr. Fauci and Dr. Birx, as well as the President, have been emphasizing contact tracking, wearing of gloves and masks, washing the hands, not touching the face, sterilizing surfaces, and social spacing, all of which are essential in relatively discrete geographic regions. But the larger picture of the pandemic is not fully understood by the public. It is in this context that we suggest changing the rules to mandate the official involvement of designated categories of academic practitioners in selected aspects of understanding and managing the dilemma.

The political situation confronting those urging substantive changes in dealing with COVID-19 is unbelievably complex. The existing federal and state programs are slow and far more expensive than they should be. Part of the explanation is political, with the President defending his turf against the Democratic Party, who have been absent from legislating in Washington DC for over a year. Additional opposition comes from largely Democratic states like New York, New Jersey, Massachusetts, and California whose legislators have been rashly increasing salaries for unionized workers and government employees for years, and now hope to diminish their state's debt through tax legislation designated as COVID-related.

In addition to these political disincentives, there is the other reality that government employees rarely lose their jobs, and are constantly reminded that they must remain passive rather than reactive towards their work and union membership. This contrasts starkly with staff members at private firms or academia who are much likelier to regard their employment with pride, and are not deterred from calling for changes when needed.

URGENT NEED TO TRAIN MANAGERS OF CLINICAL DISEASE INFECTIONS

For many years, textbooks of epidemiology discussed how infectious diseases developed and recommended how epidemics should be dealt with. But, in recent decades, medical students are no longer taught much about the clinical diagnosis and management of infectious diseases. It is crucial that our medical schools now examine what they are teaching, what they are ignoring, and upgrade the capabilities of their students in controlling the major infectious diseases. Two

basic courses should be reintroduced into the medical and nursing curriculum as soon as possible:

a) Principles and Clinical Practice of Immunology and Virology
b) Principles and Clinical Practice of Clinical Epidemiology

The large majority of federal and state health agency employees are no longer well trained in dealing with infectious outbreaks, and their leadership is more familiar with public health theories than the complex details of dealing with real-time epidemics. The same may be the case in hospitals, many of which lack staffs with actual experience in epidemics. The consequence is that the public turns to the federal government for leadership and guidance whenever such dreaded conditions arise.

When a nation of more than 300,000,000 residents, extending over thousands of miles and diverse in so many respects, confronts a war or natural calamity, it expects the government to deal with the threat. But when the event is very rare, the most competent government will often demonstrate its inexperience and awkward incompetence in taking on such a responsibility. The President has shown remarkable talent in reviving the American economy and dealing with foreign adversaries, but has had little experience in health matters. For the latter, he must rely on the federal health agencies and his personal advisors. I hope that some of the suggestions in this volume will prove of practical value to him and the country in addressing such problems.

In the paragraphs above, we suggest that a third source of knowledge and advice should be called upon when complex health and disease issues arise. In supplementing the input of

the federal health agencies and the President's advisers, full-time clinically experienced physicians who are teaching and studying human disease at our medical and public health schools should be identified, vetted, and listed as fully qualified participants in responding to specific health-related emergencies. Their voices would reflect the scientific views of true experts, largely without the job-related, and sometimes conflicting views, of government agencies. Our approach is described briefly below.

EPIDEMIOLOGICAL APPROACH TO COVID-19 AND OTHER EPIDEMICS

We would like to suggest an approach that is compatible with our other recommendations for the promising future of public health. Details of the plan are described in various chapters of this volume, summarized in Chapter 19, to which we hope the readers will refer.

Our basic recommendation is establishing a comprehensive **Clinical Public Health Department** in an existing medical or public health school, within which there would be a Health Statistics Center. The department itself would be an autonomous division of the parent university, offering MPH and PhD degrees as well as other programs to physicians and nurses who have had intensive experience in clinical practice, and wish to devote their future careers to teaching and epidemiological research in human health and disease. The faculty would consist of a core of well-trained clinician-epidemiologists, broadly experienced nurses, biostatisticians, computer technicians with a strong interest in health research, and a diverse staff of office managers, data entry clerks, patient interviewers, and others as required by the department's teaching, research, and ancillary programs.

The Health Statistics Center would become, in part, the department's fee-based agency for calculating epidemiologically valid health statistics for city, state, and federal health bureaus. Modeled after the unique rapid-reporting cancer registration system established by us for the State of Maryland, its staff would visit all the region's hospitals, communicate regularly with all physicians treating patients, and review the news media to identify any patients with the virus or disease of interest. This system succeeded in identifying the large majority of Maryland patients developing cancer within a week or two of initial diagnosis, hospitalization, or death. In this new setting, the center could identify the large majority of, for example, COVID-19 patients diagnosed, hospitalized, or dying, and classify them by age, sex, race, and the co-morbidity of other diseases. After a current crisis is resolved, the center could target another disease for investigation, or resume its routine cancer registration operations.

If national, rather than regional, statistics on a disease or epidemic were needed, the Health Statistics Center could establish temporary units in half a dozen regions of the country to yield statistically valid national rate estimates. In the long run, however, the optimal solution would be to gradually increase the number of Clinical Public Health Departments and Health Statistics Centers at appropriate medical or public health schools around the country.

The underlying formula should remain unchanged: The Clinical Public Health Departments and their Health Statistics Centers should maintain their autonomy as academic units of the universities, rather than become subjected to the supervision of a federal or local government agency. This legal structure and operating mode will guarantee its

academic identification, protect it from much political opposition, and allay the faculty of anxiety about being swallowed up by a governmental agency and losing their *raison d'être*.

In serving as the Health Statistics Center for a geographical region of the United States, the center would become the repository of hard data relating to an epidemic, a pandemic, or some other catastrophic event. As a designated agency for collecting statistical data on the diseases of interest, the Center would eventually become a major information source for the President, his advisers, and the directors of the major federal health agencies who are, to a large extent, politically rather than scientifically driven.

Our proposal for establishing the Clinical Public Health Departments and Health Statistics Centers will greatly benefit the geographical region, as well as the nation as a whole.

This will enhance our ability to deal with future medical dilemmas, facilitate epidemiologic research on human disease, and attract physicians and nurses of the highest quality into lifetime careers in teaching and advancing public health.

THE PROMISING FUTURE

CHAPTER THIRTEEN SUMMARY

COST AND QUALITY OF DERMATOLOGICAL CARE BY BOARD-CERTIFIED DERMATOLOGISTS AND FAMILY PHYSICIANS

Shortly after dermatology achieved departmental status at the University of Maryland, Dr. Joseph W. Burnett was appointed its chairman. As a clinical leader he was unusually receptive to classical biomedical research, and an agreement between the Departments of Preventive Medicine and Dermatology quickly led to an agreement to cooperate closely on investigations of mutual interest in dermatology. Undertaking an epidemiological comparison of dermatological care by board-certified dermatologists and family physicians came immediately to mind, as a research topic of interest and value to the public, the medical profession, health insurance companies, and the government. To our knowledge, no studies of this kind had ever been conducted. The topic deals with the super-sensitive matters of price and quality of dermatological care, subjects of concern to everyone.

Months were devoted to asserting and debating the details of the proposed study, which would involve the American Academy of Dermatology as well as the three participating departments of the medical school. In the final agreement, it was decided to undertake a prospective study of patients suffering from any of 17 dermatological conditions followed for six months. There was, in addition, the possibility to follow up with a larger, definitive study after the preliminary

results were evaluated, if approved by the American Academy of Dermatology and the American Board of Family Medicine.

This study by two competitive specialty groups within medicine was a bold attempt to subject such sensitive topics to objective epidemiological investigation. More studies of this kind need to be undertaken to monitor the costs and quality of a variety of diseases and numerous other aspects of clinical medicine. In our view, the clinically trained faculties of Clinical Public Health Departments recommended in this book are the best suited to plan, conduct, and analyze such investigations.

CHAPTER THIRTEEN

COST AND QUALITY OF DERMATOLOGICAL CARE BY BOARD-CERTIFIED DERMATOLOGISTS AND FAMILY PHYSICIANS COMPARED

BACKGROUND

During my tenure at the University of Maryland, dermatology was elevated to departmental status there and in other medical schools around the country. Dr. Joseph Burnett, the designated chairman, stood out among his colleagues nationally as being unusually interested in basic science and epidemiologically relevant research on dermatological diseases. This presented us with a number of unusual research opportunities. One was to conduct a study in which the practice patterns, outcomes, and cost-effectiveness of dermatological care provided by board-certified dermatologists would be compared with the care offered by family physicians. A second opportunity was to create a user-friendly automated PC-based clinical information system for practicing dermatologists, to be approved by the American Academy of Dermatology. A third was to develop a teledermatology system to permit the examination, treatment, and follow-up of specific categories of dermatology patients seen at sites remote from the dermatology clinics at the medical school.

Three years were devoted to preparing for these projects, including the complex task of allaying the anxieties of two competing medical specialties to allow a comparative study. Data collection for the first of these proposals was initiated during a period in which a degree of uneasiness about the study appeared among both groups of the dermatology and family medicine participants. This was to be expected, since no study had ever before been undertaken to compare the advantages and disadvantages of patients seeking medical care from two dynamic and enterprising clinical specialties.

If the Clinical Public Health Departments we recommend are established, experienced epidemiologists could play significant roles in a host of medical care issues. We present here the detailed designs of three dermatological investigations negotiated with Dr. Burnett, which CPH experts could consider as prototypes for their own studies. Objective and valid data are urgently needed at a time when so many healthcare dilemmas require real-life solutions, rather than evasion or political compromise. A year or two after completing these ventures, I decided to terminate my half-century of epidemiological enterprises, with the earnest hope that this approach can be rejuvenated by another handful of epidemiological pioneers in the near future.

Comparisons between the cost and effectiveness of many aspects of dermatological care by board-certified dermatologists and family physicians have been a subject of conjecture and dinner discussions for many years. Resolving it, or at least subjecting it to formal study, has always faced the rivalries expected between two closely related medical specialties. In the early 1990s, circumstances arose to permit us to design and carry out a controlled comparative study of care by dermatologists and family physicians after a succession of

meetings were held between officials of the American Academy of Dermatology, Dr. Joseph Burnett and Dr. Edward Kowalewski—chairmen of the Departments of Dermatology and Family Medicine at the University of Maryland. The Academy representative and the two clinical chairmen maintained a respectful and open attitude throughout the successive stages of the project, although each was aware of the potential hazards of the study and its findings to their own specialty.

Evaluating the costs and clinical effectiveness of medical care has stirred a host of emotions and controversy in medicine for many years. In our case, it was the dermatology chairman at Maryland, Dr. Joseph Burnett, whose character, reputation, and diplomatic talents made it feasible to undertake this seemingly impossible effort. And, to some extent, it was I, a clinically trained physician with epidemiological training, who was able to guide the conversations, exchange ideas, and allay some of the anxieties of the clinical competitors in this unusual enterprise.

DESIGN

The participants proposed to design and implement an epidemiological study to generate valid estimates of the practice patterns, clinical outcomes, and cost-effectiveness of treating demographically similar patients with a chief complaint of any one of 17 dermatologic conditions, by board-certified dermatologists and board-certified family physicians. The analysis was aimed at establishing objective quantitative estimates of the following parameters for patients with each of the specified skin conditions:

1. **Number of patient visits required in order to reach a definitive diagnosis**
2. **Number of diagnostic tests administered before initiating definitive therapy**
3. **Cost of diagnostic procedures before initiating definitive therapy ***
4. **Time elapsed between initial visit and definitive outcome**
5. **Number of different drugs prescribed for the condition until definitive outcome achieved.**
6. **Cost of drugs prescribed for the condition until definitive outcome achieved ***
7. **Cost of all other treatments prescribed for the condition until definitive outcome achieved ***
8. **Cost to diagnose the condition and bring about its remission or clinical stabilization ***
9. **Proportion of patients with each of the skin conditions treated by dermatologists or family physicians that express satisfaction with the manner in which their condition was diagnosed.**
10. **Number of patient visits to dermatologists or family physicians by patients with each of the skin conditions during the study.**
11. **Proportion of patients seen by dermatologists or family physicians that express satisfaction with the manner in which their condition was treated.**
12. **Number of work or school days (including those required for physician visits) lost because of the skin condition, over a six-month observation period.**
13. **Efficiency of achieving the definitive diagnosis (process measures).**
14. **Efficiency of achieving the definitive treatment (process measures).**

15. Cost-effectiveness of diagnosing and treating the condition by dermatologists and by family physicians (process measures).

*** Total standardized to uniform base**

The study was designed to provide, within the limitations of a modest budget and relatively brief time span, epidemiologically valid estimates of a number of cost-effectiveness measures for dermatologic care, as provided by dermatologists and family physicians in the ambulatory care setting. Methodologically, the investigation followed a classical prospective design, in which the clinical practices and eligible patients of the participating dermatologists and family physicians were followed over a six-month observation period.

Approximately 1,000 patients undergoing diagnosis and treatment for any of 17 specific dermatological conditions, and representing the total number of such patients seen by the participating physicians over a continuous time span, were selected from patients currently seeking care from a representative sample of community-based and board-certified dermatologists and family physicians in the Metropolitan Baltimore region. The patients were described, characterized, and followed for six months by means of regular weekly review and abstraction of their physicians' clinical and administrative records, as well as by personal interview. The clinical course of their dermatological conditions, from diagnosis to treatment to definitive outcome at six months, as well as their level of satisfaction and a number of quantitative and qualitative process and cost measures were evaluated, and comparisons between the dermatological care rendered by the sampled dermatologists and family physicians were drawn.

Because this study was the first of its kind in dermatologic care, and because of its limited funding and duration, a number of important issues relating to practice patterns, outcomes, and cost-effectiveness of dermatological practice were unaddressed and will require new investigations in the future. In order to design and plan for the full-scale definitive study to follow, it was essential that all data collection protocols, methodologies, and clinical outcomes of the initial study were fully assimilated, objectively critiqued, and appropriate conclusions were drawn. To this end, a Planning and Monitoring Panel (PMP) was established, with two principal objectives: (a) to monitor, assimilate, and analyze all relevant details of the study, including its conduct and findings; and (b) to plan for a definitive investigation, which would be sponsored by the American Academy of Dermatology and the American Board of Family Medicine.

To minimize bias and achieve a satisfactory degree of scientific validity, it was essential that the following conditions be met:

1. **The two physician groups should be as representative as possible of practicing physicians in the community**, so that the findings can be generalized to dermatologists and family physicians in Metropolitan Baltimore;
2. **Patients seeking dermatological care from the selected physicians should be as representative as possible of the universe of such patients in the community**, so that the study results can be generalized; and
3. **Study patients visiting the sampled dermatologists should be as similar as possible to those visiting the**

family physicians in respect to all characteristics that might affect the study outcomes.

In order to satisfy the above conditions, the following design decisions were made:

1. **Broadly based pools of Baltimore-region dermatologists and family physicians were drawn up**, including community-based physicians with privileges at community hospitals, as well as the University of Maryland Medical System and the Johns Hopkins Hospital, which assured a broad payer mix of dermatology patients;
2. **Efforts were made to select physicians from these pools who were of diverse racial and sexual composition** and who were deemed likely to treat a wide range of patients—white, black, and Asian from all social classes; and
3. **Charity patients and others treated by residents in hospital clinics were excluded** because their inclusion would increase the complexity of the analysis, as well as the number of patients required for the preliminary study.

With the active cooperation of the chairman of dermatology at the University of Maryland, presentations on the proposed study were made to groups of dermatologists, from which a sufficient number of community-based dermatology practitioners were then recruited for the study. Criteria for their selection included:

1. Certification by the American Board of Dermatology;
2. Community-based practice in Metropolitan Baltimore;

3. At least 50% of their patients estimated to be fee-for-service, or insured by Blue Cross or commercial health insurance, without restriction as to choice of physician; and
4. An expressed willingness to participate fully in the study, including the granting of access to their clinical and administrative records throughout the study year.

With the cooperation of the chairman of family medicine at the University of Maryland, a large pool of community-based family physicians was made available and a sufficient number of practitioners were recruited for participation in the study. Criteria for their selection included:

1. Board certification in family medicine;
2. Community-based practice of family medicine in Metropolitan Baltimore;
3. At least 50% of their patients estimated to be fee-for service, or insured by Blue Cross or commercial health insurance, without restrictions as to choice of physician; and
4. An expressed willingness to participate fully in the study, including the granting of access to their clinical and administrative records throughout the study year.

Because of the relatively limited budget for the study, the investigational design was simplified by excluding charity and other uninsured patients who are often seen by hospital residents, and by limiting the participation of patients insured through an HMO or those whose insurance required them to undergo triage by a generalist before referral to a physician of choice for treatment of their skin condition.

Seventeen dermatological conditions were selected to represent the diagnostic and therapeutic challenges of dermatologists in their everyday practice. These 17 "monitor conditions" are commonly seen in most dermatological and family medicine practices, and thus provide a basis for valid epidemiologic comparisons between dermatological and family physicians in their management of skin-care problems. Included are the following:

1. Acne
2. Acne rosacea
3. Actinic keratosis
4. Drug eruption
5. Eczema (atopic, dyshidrotic, nummular, and contact)
6. Folliculitis, carbuncle, and furuncle
7. Fungal infections, including tinea versicolor
8. Herpes simplex and zoster
9. Molluscum
10. Pigmented lesions
11. Psoriasis
12. Scabies
13. Seborrheic dermatitis
14. Seborrheic keratosis
15. Stasis dermatitis
16. Warts
17. Skin cancer

The definitive clinical outcome was defined as the clinical state of the monitor condition at the end of the six-month observation period, i.e. cured, remitted, greatly improved, improved, slightly improved, unchanged, or worsened. This definition may be modified as experience is gained with the clinical records maintained by the participating dermatologists and family physicians.

Once each week, specially trained clinical abstracters will visit the offices of each participating dermatologist and family physician in order to collect the requisite clinical and administrative data for the study. Working closely with the physician's office manager or nurse, the abstracter will compile the requisite information for all selected patients with any of the 17 monitor conditions who have visited the office since the abstracter's previous visit. New patients, and other patients with a new dermatological chief complaint including any monitor condition, would be assigned a study number and have their demographic characteristics, dermatological condition, and all diagnostic and treatment procedures recorded. Existing patients with recurrent or persistent monitor conditions will also be included, but analyzed separately. The data to be abstracted on all eligible patients include the following:

A. Identifying Information:

1. Study number (incorporating IDs of physician and patient)
2. Visit date
3. Name
4. Date of birth
5. Sex
6. Race
7. Insurance (type, plan, payer category)
8. New or existing patient
9. Self-referred or referred patient

B. Monitor Condition:

1. Condition
2. International Classification of Diseases ICD9 Code
3. Condition new or treated

4. If new: date condition first noted by patient
5. If treated: date of latest clinical manifestation

C. Diagnostic Process:

1. Diagnostic procedures at this visit
2. ICD9 Code/Name/Charge
3. ICD9 Code/Name/Charge
4. ICD9 Code/Name/Charge

D. Treatment Process:

1. Treatment at this visit
2. ICD9 Code/Name/Charge
3. ICD9 Code/Name/Charge
4. ICD9 Code/Name/Charge
5. ICD9 Code/Name/Charge
6. ICD9 Code/Name/Charge

E. Clinical Assessment:

1. State of monitor condition at this visit:
Cured/Remitted/Greatly improved/Improved/Slightly improved/
Unchanged/Slightly worse/Much worse

2. Bill for services (for visit/examination/tests/procedures)

Shortly after entry into the study, and six months later, each patient will be interviewed by a trained and experienced interviewer. The following information and personal opinions will be sought:

F. Identifying Data:

1. Study number
2. Interview date & time
3. Name
4. Birth date
5. Dermatological Condition

G. Questions for all patients:

1. "How would you rate the treatment of your skin condition by the Dermstudy Doctor?" (Excellent/Good/Fair/Poor)
2. "How optimistic are you that this condition has been effectively treated?" (Very/Somewhat/Little/Not at all)
3. "Would you go to your Dermstudy Doctor again for treatment of this or any other skin condition?" (Yes/Unsure/No)
4. "Would you recommend your Dermstudy Doctor to your family and friends?" (Yes/Unsure/No)
5. "How many days of work or school (or other planned activity—counting doctor visits) did you lose because of the skin condition?" ( )
6. "To what extent did your HMO or health insurance plan dictate the kind of physician you visited for this condition?" (Totally/Partially/Not at all)
7. "How important to you is the specialty of the physician you visit for skin care problem?" (Very/Somewhat/Little/Not at all)
8. "How important to you is the personality of the physician you visit for skin care problems?" (Very/Somewhat/Little/Not at all)
9. "How important to you is the waiting time in the office of the physician you visit for skin care problems?" (Very/Somewhat/Little/Not at all)

10. "How important to you is the possibility of choosing your own physician for skin care problems?" (Very/Somewhat/Little/Not at all)

H. Questions for patients who had previous occurrences of the monitor condition:

1. "What type of physician did you visit for the previous occurrence of this condition?" (Dermatologist/Family physician/Other)
2. "Why this physician?" (Record reason)

ANALYSIS

The analysis seeks to establish quantitative estimates of a number of parameters for patients with each of the 17 monitor skin conditions or combinations thereof, which are treated by community-based dermatologists and family physicians. All patients will be followed prospectively from their initial diagnostic visit for the monitor condition over a six-month period of time, at the conclusion of which their definitive clinical outcome will be recorded. The latter will preferably be generated from the clinical record; however, patients who, for whatever reason, do not return to their physicians will have the clinical outcome self-recorded by the patients at the time of their six-month follow-up interview.

Major analytical cross-tabulations in which the dermatologists are compared with the family physicians, include the following, among others:

1. **Number of clinic visits required to reach a definitive diagnosis** of monitor condition.

2. **Number of diagnostic tests administered before initiating definitive therapy.**
3. **Total standardized cost of diagnostic procedures before initiating definitive therapy**.
4. **Number of clinic visits before reaching definitive clinical outcome.**
5. **Time (weeks/months) elapsed between initial diagnostic visit and achievement of definitive clinical outcome.**
6. **Number of drugs prescribed for the monitor condition** until the definitive clinical outcome.
7. **Total standardized cost of drugs prescribed for the monitor condition** until the definitive clinical outcome.
8. **Total standardized cost of all other treatments prescribed for the monitor condition** until the definitive clinical outcome.
9. **Total standardized cost of diagnosing the monitor condition and achieving the definitive clinical outcome**.
10. **Proportion of patients treated by dermatologists or family physicians that express satisfaction** with the manner in which their monitor condition was diagnosed.
11. **Number of work or school** (or otherwise normal activities of daily living) **days lost because of the monitor condition** over the six-month observation period.
12. **Diagnostic efficiency**, as measured by the proportion of total patients with a given monitor condition who receive a definitive diagnosis within the six-month observation period.
13. **Treatment efficiency**, as measured by the proportion of total patients with the monitor condition who attain a clinical outcome classified as cured, remitted, or greatly improved within the six-month observation period.

14. **Cost-effectiveness of the diagnostic and treatment processes** for each of the monitor conditions and all combined by dermatologists and family physicians.

DISCUSSION

The pilot study was designed, approved by all parties, and completed, as planned. The results could not be published, however, as the two clinical groups began to raise issues concerning the outcomes and publication of the findings. The dilemma of objectively reviewing the quality and costs of clinical care by two competing medical specialties has obviously not yet been resolved. For us, however, the project was a success, as our effort to bring together two competing groups of physicians and objectively evaluate important aspects of their diagnostic and therapeutic procedures was actually conducted. We hope that this precedent has now been set, that other properly designed and well-controlled epidemiological evaluations of healthcare by diverse groups of physicians will be undertaken.

The setting for such studies in the future would have to be a fully staffed school of public health or medical school department of public health, with an adequate number of full-time clinically trained faculty, statisticians, and computerniks, along with staff members including patient interviewers and data processors to manage the data collection, data processing, and analytical phases of this study. In view of the paucity of such healthcare studies being undertaken these days, establishing autonomous Clinical Public Health Departments catering to the unique needs of clinically trained physicians and nurses, as we are strongly recommending, offers the most promising avenue to follow.

CHAPTER FOURTEEN SUMMARY

DEVELOPING A CLINICAL INFORMATION SYSTEM FOR DERMATOLOGISTS

Early in the computer age, hospitals began to recognize the potential benefits of automating their clinical information systems to allow rapid access and enhance the processing of their data. At that time, most medical centers had relatively simple record rooms and few employees with substantial computer training. This encouraged private companies to recruit individuals with basic computer training, and offer to develop clinical information systems for hospitals and practitioners.

A large majority of the commercial companies had no physicians or clinically trained epidemiologists with experience in hospital affairs among their personnel. Their firms were designed to appeal to the medical centers with their technical expertise in computer operations, talented sales personnel, and large budgets to produce and market attractive sales promotion paraphernalia. They were highly successful in these efforts, and no academic medical center except ours, to my knowledge, has ever previously become involved in competing with these commercial firms.

Our Department of Public Health had a fully operational Health Data Management Center, with a cadre of computerniks broadly experienced in the health arena, clinically trained epidemiologists, biostatisticians, and a large staff of data

clerks, patient interviewers, and others experienced in a variety of health and hospital-related studies. We decided to begin competing with the commercial companies in developing clinical information systems, despite a lack of funds or expertise in advertising our services and capabilities.

It was decided that our first clinical information system project would be designed for dermatologists and, if successful, expanded to other specialties. The system we created anticipates a powerful new role of medical school departments of public health and some public health schools, if they are willing to take up the challenge. Such developments, in our belief, are best undertaken by academic entities like ours, rather than commercial firms lacking clinical experience and motivated primarily by financial interests.

CHAPTER FOURTEEN

DEVELOPING A CLINICAL INFORMATION SYSTEM FOR DERMATOLOGISTS

BACKGROUND

Our interest in creating computerized medical record systems was stimulated by the unique advantages of such systems to satisfy the needs of clinicians and biomedical researchers. Patients seen in hospital, clinic, or office settings usually appear with a multiplicity of diseases, conditions, signs, and symptoms, only some of which relate to the current medical visit. A well-designed computerized system assures that patient data from all physician contacts in the system would be available at every visit. For the epidemiological researcher, such a system will permit an optimal randomized selection of patients and controls, as well as other refinements, in organizing, conducting, and publishing many types of disease-related studies.

At medical facilities these days there is an effort to limit physician contact with patients by focusing on a chief complaint, in order to reduce expenses and maximize income for the practice. Such a policy does temporarily reduce costs but, in the long run, adds to the expense of diagnosing and treating all other illnesses suffered by the patients.

After establishing a computerized clinical information system, the management and outcomes of all medical conditions

experienced by the patients can be readily evaluated, both clinically and epidemiologically. The costs borne by the patient, the insurer, and third-party payers can also be assessed, as well as the physician's notes and patient's comments concerning the clinical management, disease outcomes, and level of satisfaction with the service.

As the Computer Age began to mature, academic physicians, government officials, and private companies began to recognize the advantages of computerized medical records over the largely manual systems then in use. Among the benefits of automation were the following:

1. **Rapid availability, at any time, of each patient's medical record** and associated administrative information for physicians, hospitals, and others involved in the patient's care.
2. **Advantages in undertaking the clinical and epidemiological analyses of the diseases of interest**, their risk factors, rapidity of arriving at a definitive diagnosis, therapies, and the patients' opinions of their healthcare services.
3. **Analysis of costs to patients, insurers, and third-party payers.**
4. **Greater security of the medical records** from alteration, manipulation, and theft than with less automated systems.
5. **Reduction in costs of maintaining patient medical records** after the system is fully established.
6. **Enhanced opportunities for effective communication between patients, caregivers, and family members.**

The comparative study of dermatological care, described in Chapter 13, was undertaken to serve as the initial data input

for an automated information system to be developed by the Health Data Management Center (HDMC) of the Department of Preventive Medicine. Our interest arose during the early years of data systems development, when rapid advances were being made in computer technology, and hospitals were solicited to have computerized data systems developed by commercial companies without hospital-based physicians and others with a direct knowledge of hospital-based operations. It was our belief that departments such as ours, with its strong cadre of epidemiologists, clinicians, computerniks and statisticians could readily compete with the private firms in developing hospital information systems. In our view, we need only the funds for advertising and promoting our services to initiate the service.

DESIGN

We set out to develop a clinical information system designed to enable dermatologists to record, retrieve, tabulate, and analyze the clinical, epidemiologic, and demographic information of their patients, as well as to facilitate research on dermatologic diseases and possibly other relevant modalities of clinical practice. Each dermatologist's personal computer would serve as a spoke in a network that would telecommunicate with a central hub, or server, in the metropolitan area of the practice. The local hub, in turn, could ultimately be linked to a national hub in which clinical and research data from all localities would flow, and from which continuing medical education programs, health technology assessment reports, and other activities would be transmitted. The system could be developed over a few years in stepwise fashion, beginning as a client–server system in Baltimore, proceeding to three interactive hubs in Baltimore, Chicago, and Boston, and eventually maturing into a national (and,

possibly, international) clinical information system for dermatology.

The principal benefit to the participating dermatologists will be the ease with which they can record and retrieve clinical information on their patients, classified in a multiplicity of ways, including specific dermatologic condition, demographic attributes, and occupational, dietary and exposure histories, as well as epidemiologic risk factors and healthcare characteristics that affect the cost of practice. The rapid availability of the computer-generated information would enable each dermatologist to analyze his or her clinical practice and decide on the most effective ways to maintain or improve its quality and control of costs.

Benefits to the Academy of Dermatology, which agreed to fund the project's initial phase, would include the ability to conduct controlled studies of dermatological care. The latter—incorporating such issues as quality, costs, and causal factors of disease—could be conducted rapidly, with minimal intrusion into each dermatologist's practice and at substantially reduced research costs. Other advantages would include:

1. **Organizing continuing medical education programs**, with immediate feedback from the clinician participants.
2. **Rapid two-way teleconferencing and polling of membership** on important issues for the Academy.
3. **Transmitting health technology assessment reports on dermatologic practice**, in response to requests from individual practitioners.

Since the information system would be controlled (and, possibly, owned) by the Academy, responsibility for sales and

leases of other products of the system to dermatologists, hospitals, medical schools, and government agencies would reside with the Academy, though perhaps administered through an agreement with the Department of Preventive Medicine. The latter would be responsible for system development, software adaptations, user training, systems maintenance, and periodic upgrading.

The Academy would lease the software and network rights to participating dermatologists for an annual rate to be determined in consultation with the Department of Preventive Medicine. The rates might vary with such parameters as the dermatologist's years in practice, rural/urban setting, willingness to participate in Academy-approved studies, networking costs, and other factors to be determined. The dermatologists would employ their own staff members to record the clinical data, retrieve the analyses, and assume responsibility for all routine functions of the system.

The staffs of the participating dermatologists would be trained by members of our Department of Preventive Medicine as part of the lease agreement. On a regular basis, perhaps once a week, they would key in the requisite clinical and administrative data of the practice. The inputted data would be edited and validated by software produced by the Department, in accordance with policies and procedures agreed to by the Academy. Training programs for all personnel assigned to the project would be the responsibility of the Department.

The clinical information system would serve:

1. As the clinical information processor for each participating dermatologist;

2. As the pathway for all clinical and cost-related research in dermatology by the Academy;
3. As the principle medium for continuing medical education in dermatology;
4. As an interactive telecommunication and teleconferencing center for the Academy; and
5. As a provider of health technology assessment services to the dermatological profession at large.

The Clinical Information System: Following procedures to be developed by Department of Preventive Medicine faculty responsible for developing and maintaining the clinical information system, essential information on patients under the care of each participating dermatologist would be keyed into the system by a designated clerk from each practice. Included would be diagnostic, therapeutic, and cost information, as well as other items deemed relevant to the cost and effectiveness of treating dermatology patients.

Initially, some of the data entered would be abstracted from the earlier comparative study of dermatology and family medicine described in Chapter 13. This information would remain strictly within each practitioner's purview, not to be disclosed or utilized by others without their express permission. However, summary data in graphical or tabular form would be available on a regular basis. The system would also identify outliers among the patients, which may be of interest in evaluating the cost and quality of the dermatological services provided.

After the information system has been fully developed, tested, and validated, Phase One of the project would involve setting up a 25-unit client–server system for participating Baltimore dermatologists. Using software developed by the HDMC,

each dermatologist or designated staff assistant would become capable of performing the following in stand-alone mode:

1. **Enter clinical information on all patients** in standardized fashion;
2. **Verify, edit, and validate all clinical information** entered;
3. **Produce tables, graphs, and other summary data relating to the patients**, according to a variety of predetermined variables of interest (e.g. age, sex, race, disease, exposures, drugs, treatments, outcomes, costs, etc.); and
4. **Assemble clinical data on patients selected for study by the Academy** and edit the data prior to submission to the Department's Health Technology Cooperative for processing and analysis.

A second phase of the project would involve setting up client–server systems for dermatologists in Boston and Chicago. In a third phase, a national system of intercommunicating client–server systems would be established in cities throughout the United States, and, if approved, this model could be extended to other clinical specialties.

Research on Dermatological Practice: The networking and telecommunication capabilities of the system would enable the Academy of Dermatology to undertake, at relatively modest cost, epidemiologically valid studies on the cost-effectiveness of dermatological practice, as well as investigations of risk factors in skin disease and clinical trials of new technologies. Examples of possible investigations would include:

1. **Trials to develop, test, and validate a severity of illness scoring system** to control for case mix differences in dermatological practice;
2. **Assessments of clinical efficiency or cost-effectiveness** among appropriately selected samples of dermatologists; and
3. **Investigations of suspected risk factors in the pathogenesis of specific dermatological diseases or conditions**. The cost of such studies would be substantially lower than similar studies by clinical groups utilizing private or governmental funds. The studies would also be much easier to undertake, less obtrusive to the clinical practices of the participating dermatologists, and more expeditiously analyzed and published.

Continuing Dermatological Education: The communications capabilities of the clinical information system would easily lend themselves to adopting continuing education programs sponsored and accredited by the Academy of Dermatology. These would entail the transmission of text, tables, and (eventually) graphical materials from the Academy to the membership, and the transmission of comments, responses to questions, and other reactions from the dermatologists back to the Academy. The programs could be accessed at times suitable for the convenience of the practitioners, and their responses could be automatically processed and entered into the Academy's records for administrative, legal, and other purposes.

Interactive Teleconferencing Services: The system would provide the Academy with a rapid means of communicating with the membership, undertaking polls on important policy and practice issues, holding video conferences, and issuing

announcements, etc. The Academy might also consider developing a news channel for dermatologists and encouraging individual practitioners to communicate with each other on dermatological practice and related issues. Some of these activities would be compatible with commercial sponsorship and advertisements by vendors of health-related products and services for dermatology.

Health Technology Assessment Service: A health technology assessment service for dermatological practice could be offered by the department in cooperation with the Academy. This would provide epidemiologically valid evaluations of new drugs, devices, diagnostic procedures, surgical treatments, and other technologies for dermatological practice in a relatively short turnaround time. The assessments would be based on epidemiologically valid reviews and evaluations of the new technologies, as gleaned from recently published and unpublished literature, as well as on direct communication with the developers and early users of the technology. The latest meta-analytic techniques might also be employed to graphically summarize the scientific evidence on the utility, clinical effectiveness, maturity, reliability, regulatory status, cost, and third-party payer coverage of the technology.

ANALYSIS AND DISCUSSION

Just as our development of the Maryland Cancer Registry included proposals to eventually extend the system to include other diseases beyond cancer, our plans for the dermatological information system include an eventual extension of the technology and programmatic elements to other clinical entities. In retrospect, our department might have been too early on the scene to standardize clinical information management in this manner. It is our hope that a new

generation of clinical epidemiologists will come to realize the enormous benefits to medicine that automated systems developed by them, with the cooperation of their clinical colleagues, could achieve. The alternate pathway, already well underway, of relying on commercial companies lacking in medical and epidemiological expertise will inevitably yield products of lesser value at substantially higher cost.

Our proposals to the Academy of Dermatology were made at a time when advances in computer technology were encouraging private companies, large and small, to offer their services in developing clinical information systems for hospitals, government, and practicing physicians. At the same time, it was unfortunate that so many medical center directors and heads of public health schools and departments of preventive medicine were insufficiently knowledgeable in computer technology as to become infatuated with the theoretical cost savings of computer information systems. This often blinded them to the inherent advantages of relying on departments like ours, and on our clinically trained epidemiologists, rather than paying enormous fees to for-profit companies for developing urgently needed computer-based information systems.

More than a quarter-century has elapsed since thousands of hospitals began receiving proposals from commercial companies to computerize their medical data. University hospital centers often paid millions of dollars for new, and often fault-laden, systems. The proposers were, almost always, commercial companies lacking in medical, clinical, and epidemiological expertise. It is now time for the public health schools and departments of public health to expand their faculties with clinically experienced epidemiologists and computer specialists to compete with the for-profit developers

of information systems. Our modest level of success in this arena could grow substantially, if the medical and public health professions will learn from our experience. Furthermore, a number of our suggestions for new ventures in public health, if accepted, will stabilize the finances of many public health schools and preventive medicine departments.

The bids we made to develop computerized patient-information systems were developed by faculty members with years of experience in medical research and utilizing hospital data systems. Our prices were often lower than those of the medically inexperienced commercial competitors. However, selling products in a capitalistic society requires salesmanship skills, an arena in which academic departments like ours have long been inactive.

In closing this chapter, we again remind the reader that the sudden death of our university president—an unusually strong supporter of public health—was the cudgel that ended our promising venture in epidemiology. We continue to hope that a young and vigorous cadre of the nation's biomedical community will come to fully understand the value of epidemiological reasoning and practice in medical science. May they also boldly compete with commercial enterprises in developing health information systems, and in other arenas of their expertise in health and disease!

CHAPTER FIFTEEN SUMMARY

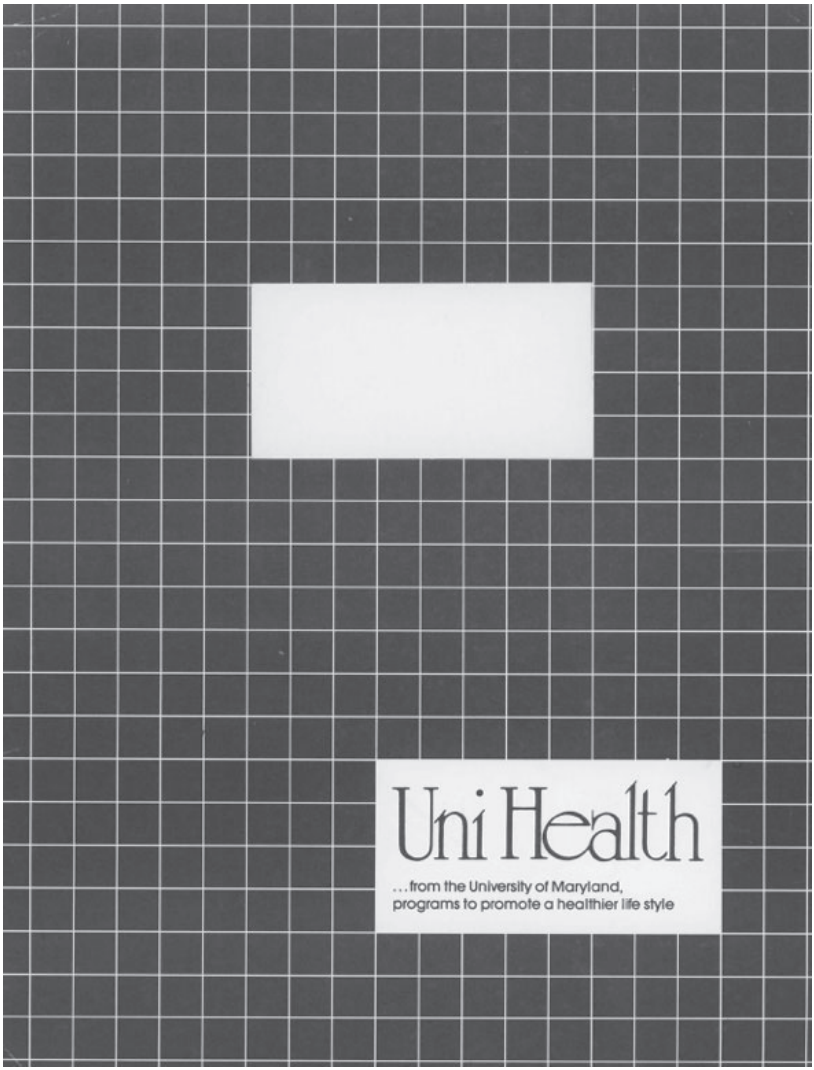
HEALTH RISK ASSESSMENT AND HEALTH PROMOTION

A variety of programs to assess and reduce the health risks of individuals began to be offered to the public early in the present era. Gymnasia and spas opened everywhere, physicians began requesting that their patients fill out health questionnaires, and government agencies launched efforts to promote health and counteract negative behaviors. Commercial efforts to sell health-promoting products on television and the print media became almost endless.

Our department, with its multidisciplinary faculty and staff involved full-time in health-related activities, was a logical home base for programs in health promotion and health risk assessment. Several years of effort led to the development of UniHealth, the department's major contribution to that era's health promotion efforts. The program had four principal components: (1) a computerized health risk assessment questionnaire; (2) a personal health profile and prescription; (3) a corporate health risk assessment; and (4) an array of educational and medical workshops designed to promote health and deter disease.

The development of the UniHealth program exemplifies another important public health activity that should not be left solely to for-profit institutions for exploitation. Public health schools and departments of public health are fully capable of

playing leading roles in this arena, provided that, as we have been recommending throughout this volume, they expand their faculties by recruiting clinically trained epidemiologists and encouraging their leadership to compete with commercial enterprises in offering health-related services to the public. We believe that innovations such as these will help attract many young physicians and nurses who have an interest in public health careers.



CHAPTER FIFTEEN

HEALTH RISK ASSESSMENT AND HEALTH PROMOTION

BACKGROUND

In the 1980s, a potpourri of initiatives to stimulate health promotion and health risk assessment began to multiply in the United States. Spas and gymnasia opened everywhere, physicians began requesting that their patients fill out health questionnaires, and government agencies launched national campaigns to publicize positive and negative actions that affect public health. Commercial advertisements on television and in the print media for a vitamin, or against a glutenous or otherwise undesirable foodstuff, were almost unending.

Our department, with its multidisciplinary faculty dedicated full-time to significant public health activities, was a logical home base for launching initiatives in health risk assessment and health promotion. In 1972, the department was selected as one of the first clinical centers for the Multiple Risk Factor Intervention Trial (MRFIT), a study on the prevention of coronary heart disease in the general population. At the same time, the department developed the now standard "stepped care" approach to hypertension control, evolving from the Hypertension Detection and Follow-Up Program (HDFP), begun in 1971.

Shortly after my arrival, we began to develop health promotion programs modified to fit the needs of gymnasia, spas, physician groups, and government agencies, although, as already noted, the department suffered from inadequate salesmanship, ineffective public relations, and a lack of political support. Our efforts are described in some detail here, in the belief that they suggest avenues for offering viable and low-cost means of health promotion and health risk assessment for the general public.

Medical school-based preventive medicine departments like ours are a most appropriate setting for health promotion and health risk assessment initiatives. Consider the factors that most would agree are necessary elements for success in such ventures. For several decades this department recruited, trained, and supervised dozens of nurses, college graduates, homemakers, and others for interviewing patients in epidemiological studies, and visiting hospitals and clinics to abstract clinical data for a variety of purposes, including the Maryland Cancer Registry, and a multiplicity of other research activities. We rarely had to advertise to recruit such staff members.

Departments like ours were a home base for clinically trained epidemiologists, social scientists, and biostatisticians, who were equipped to develop, test, and utilize health promotional and health risk assessment tools for research purposes or for lay people interested in health promotion. Our highly trained faculty members engaged in research activities and medical school teaching programs on a regular basis, but were also available to participate in initiatives such as the department's health promotion and health risk assessment programs.

A new category of department staff members are the computerniks whom we have been hiring and adapting to departmental research and teaching since my arrival. A cadre of computerniks applying their technical skills to promoting the department's research and teaching capabilities can easily be modified to produce a gamut of products needed for health promotion and health risk assessment.

Beyond the fact that academic departments like ours already have the basic staff for such programs, they also feature two other unique advantages over commercial alternatives, in costs and program quality. There is little doubt that our department can generate health risk assessment and health promotion programs at a substantially lower cost than any commercial competitor. In addition, staff positions in industry are often temporary, with termination of employees likely when a project is completed. The latter practice discourages talented applicants interested in long-term commitment and employment.

A second issue of major concern is that commercial enterprises rarely deal with shortcomings or flaws discovered after the contracted work is completed, barring an impropriety that brings it to public attention. In contrast, an academically based program such as ours, whose faculty regards health promotion as a professional tool for advancing public health, would be far less likely to ignore or disown defects, and would be much likelier to institute rectifications when needed.

In view of the advantages of an academic home base for projects like these, why are academic departments not competing with commercial organizations for health promotion projects? A principal reason is that very few epidemiology-based departments possess the diverse faculty

makeup of ours. Second, there are few departments today where clinically trained epidemiologists who are fully engaged in classical epidemiological teaching and research hold the academic leadership. A third element is that, almost everywhere, the training of clinically proficient epidemiologists has been minimized, downgraded, or largely replaced by faculty committed to social science and diversity issues, rather than clear-cut medical topics like disease etiology, prevention, and treatment.

Our department's investment in time and effort for health promotion and health risk assessment was greatly encouraged by University President T. Albert Farmer, MD during his brief tenure in office, beginning in 1981. His strongly supportive relationship with us was focused on establishing the National Center for Health Promotion and Preventive Medicine, described in the next chapter.

UniHealth, the department's health promotion program, was developed at a time when evidence had accumulated to demonstrate that certain patterns of living and a variety of other health-related behaviors were associated with a longer, healthier, and more productive life. For example, controlling high blood pressure results in significantly fewer heart attacks and strokes, and cessation of smoking reduces the risks of lung cancer, heart disease, and other illnesses.

Weight control and physical fitness enhance one's sense of well-being, and increase one's energy and productivity. Limiting salt and sugar intake and reducing cholesterol also contribute to a healthier lifestyle. Based on such well-publicized findings, techniques were developed to help people modify their lives so that they benefit from the positive effects of healthy lifestyles.

A diversity of activities to improve health behavior was included in the term "Health Promotion." The program, with its logo "UniHealth," integrated four major components:

1. A computerized health risk assessment questionnaire;
2. A personal health profile and prescription;
3. A corporate health risk assessment program; and
4. An array of educational and medical workshops aimed at improving specific health habits.

DESIGN

The **Health Risk Assessment Questionnaire** provides a computer-based evaluation of each participant's current health status. It assembles information on the current lifestyle practices and other health-related characteristics of the individual, estimates relative risks on the basis of published epidemiological studies and mortality tables, produces a printout of the participant's disease risk factors, and summarizes that person's 10-year risk of death from the 12 most common causes of death in populations of similar age, race, and sex. Finally, it estimates each participant's overall mortality risk.

If a participant's "health age" is calculated to be greater than their chronological age, that person is deemed to be at higher overall risk during the next 10 years than an average person of the same chronological age. Conversely, if the appraised age is lower than the true age, the individual is considered at lower than average risk. Finally, and perhaps most importantly, the UniHealth printout recommends how the participant can reduce the risks and improve his or her chances of living a longer, healthier life. To complete the process, other information abstracted from employer records, physical measurements of

height, weight, and blood pressure, X-rays, and samples of blood and urine drawn for cholesterol and other critical substances are summarized, and the health implications are defined. Our original UniHealth health risk assessment form is presented in **Appendix A**.

After completing the health risk assessment, a **Personal Health Profile and Prescription** is generated for each participant. This document, which is created specifically for each individual, includes dietary, behavioral, and clinical suggestions recommended by the UniHealth program. An example of the personal health profile and prescription is presented in **Appendix B**.

A **detailed Corporate Health Risk Assessment Report** is submitted to firms signed up for this program, which is based on the personal health risk assessments submitted by all their employees (see **Appendix C**), and details concerning workshops arranged by UniHealth for the company's employees are described in **Appendix D**.

Appendix A

Health Risk Assessment Form

Uni Health ...from the University of Maryland, programs to promote a healthier life style

HEALTH RISK ASSESSMENT

Health risk assessment is an effective tool which you can use to help evaluate your health status. Your answers to the printed questions, together with the clinical and fitness test results, will generate a computerized health prescription designed especially for you. After this assessment is completed, you will have an opportunity to discuss the findings with physicians and fitness specialists from Sinai Fitness. Your employer will *not* receive any information relating specifically to *your* health. The data you provide will be processed in strictly confidential fashion by the Health Data Management Center at the University of Maryland.

Thanks for participating in this effort to promote your health!

Please enter your answers in the empty boxes, using *numbers* only.

Participant Number: 0 0 4 3 7 0 2 6

I. PERSONAL PROFILE

1. Sex [1] Male [2] Female — 2
2. Race/Origin [1] White (non-Hispanic) [2] Black (non-Hispanic) [3] Hispanic [4] American Indian or Alaskan Native [5] Asian or Pacific Islander [6] Other [7] Not sure — 1
3. Age (at last birthday) Example: 28 years old = [2][8] — 37
4. Height (Without Shoes) Example: 5 feet, 7½ inches = [5]' [0][8]" (No fractions) — 5' 09"
5. Weight (Without Shoes) Example: 139 pounds = [1][3][9] — 180
6. Marital status [1] Single (never married) [2] Married [3] Separated [4] Widowed [5] Divorced [6] Other — 5
7. Education [1] Did not graduate from high school [2] High School [3] Some College [4] College or Professional Degree — 3
8. Employment [1] Employed [2] Unemployed [3] Homemaker or Student [4] Retired, Other — 1
9. Occupation [1] Professional, Manager or Proprietor [2] Clerical or Sales [3] Craftsman or Technician [4] Service or Laborer [5] Unemployed — 1
10. What is your Postal Zip Code? — 2 1 2 7 4

II. BEHAVIORAL PROFILE

Tobacco

11. What is your smoking status at this time? [1] Smoker [2] Ex-Smoker [3] Never Smoked — 2
(If you have never smoked, skip to item 15)
12. At what age did you begin smoking? Example: Age 18 = [1][8] — 16
13. On the average, how much have you smoked each day during the past year or the last year you smoked? *Cigarettes* — 40
Cigars or Pipes
14. If you are an ex-smoker, at what age did you quit? — 37

Alcohol

15. Which category best describes you?
[1] Drink more than one drink per week
[2] Do not drink at all, but used to drink more than one drink per week
[3] Do not drink at all (or only one drink or less per week)
(If you checked Box 1, skip to item 17.) — 1
16. On the average, how much have you drunk *each week* during the past year?
Beer (bottles or cans) — 05
Wine (glasses) — 01
Mixed drinks or shots — 03

Drugs/Medications

17. How often do you use drugs or medications to elevate your mood or fight depression? [1] Almost every day [2] Sometimes [3] Rarely or never — 2

18. How often do you use drugs or medications to tranquilize or help you sleep? [1] Almost every day [2] Sometimes [3] Rarely or never — 2

19. How often do you use drugs or medications to pep you up or help you lose weight? [1] Almost every day [2] Sometimes [3] Rarely or never — 2

Dental Care

20. Do you brush your teeth every day? [1] Yes [2] No — 1

21. Do you floss your teeth every day? [1] Yes [2] No — 2

22. Do you visit your dentist at least once a year? [1] Yes [2] No — 1

Driving

23. Do you use a seat-belt? [1] Most times [2] Sometimes [3] Never — 2

24. How many miles do you drive or sit as a passenger during a year? (10,000 is average) — 1 2 0 0 2

III. NUTRITION PROFILE

25. Do you have food allergies or other dietary restrictions which limit the kinds of foods you can eat?
If yes, describe very briefly here: [1] Yes [2] No —

26. On an average day, how many times do you eat the following foods? Don't forget to include foods you eat at fast food places and restaurants.

	Times Eaten Per Average Day					
	3 or More	*2*	*1*	*Less than 1*	*Rarely or Never*	
a. Red meat (beef, lamb, pork, ham, bacon, sausage, luncheon meat, etc.)	[1]	[2]	[3]	[4]	[5]	3
b. Chicken, turkey, veal, fish, seafood	[1]	[2]	[3]	[4]	[5]	3
c. Liver, kidney, heart or other organ meats	[1]	[2]	[3]	[4]	[5]	4
d. Regular cheese, creamed cottage cheese or yogurt	[1]	[2]	[3]	[4]	[5]	2
e. Low fat cheese or yogurt	[1]	[2]	[3]	[4]	[5]	4
f. Glasses of milk	[1]	[2]	[3]	[4]	[5]	4
g. Scoops of ice cream	[1]	[2]	[3]	[4]	[5]	3
h. Eggs with yolks	[1]	[2]	[3]	[4]	[5]	3
i. Pastries, croissants, etc. (except those known to be made with polyunsaturated fat)	[1]	[2]	[3]	[4]	[5]	3
j. Carrots, melon, spinach, apricots, peaches or squash	[1]	[2]	[3]	[4]	[5]	4
k. Cabbage, cauliflower, brussels sprouts, broccoli, watercress, radishes or horseradish	[1]	[2]	[3]	[4]	[5]	4
l. Other vegetables (e.g. peas or beans)	[1]	[2]	[3]	[4]	[5]	4
m. Raw fruit	[1]	[2]	[3]	[4]	[5]	4
n. Canned fruit, or canned, fresh or frozen juices	[1]	[2]	[3]	[4]	[5]	3
o. Cereals high in fiber	[1]	[2]	[3]	[4]	[5]	5
p. Snack foods with high salt content (e.g. potato chips)	[1]	[2]	[3]	[4]	[5]	4

27. When you eat meat do you choose lean cuts? [1] Usually [2] Sometimes [3] Never [4] Do not eat red meat — 2

28. How do you usually cook meat?
[1] Broil [2] Fry [3] Other methods (roasting, braising, etc.) [4] Do not eat meat — 5

29. Do you trim the fat from red meat before cooking?
[1] Usually [2] Sometimes [3] Never [4] Do not eat red meat — 3

30. Do you remove the skin from chicken or turkey before cooking?
[1] Usually [2] Sometimes [3] Never [4] Do not eat chicken or turkey — 3

31. What kind of milk do you usually use? [1] Whole [2] 2% Fat [3] 1% Fat [4] Skim — 2

32. Which of the following do you usually use at the table?
[1] Butter [2] Stick margarine [3] Tub margarine [4] Rarely use any of these — 2

33. Which of the following do you usually use for cooking?
[1] Lard or drippings [2] Vegetable shortening [3] Cooking oil [4] Do not use cooking fat — 3

34. Do you add salt to your food at the table?
[1] Usually [2] Sometimes [3] Rarely [4] Never — 1

35. Do you add salt in cooking your food?
[1] Usually [2] Sometimes [3] Rarely [4] Never — 2

36. Do you eat processed foods? (Canned soups, luncheon meats, etc.)
[1] Usually [2] Sometimes [3] Rarely [4] Never — 2

37. Do you take:
a. Multivitamins [1] Regularly [2] Sometimes [3] Rarely [4] Never — 2
b. Calcium supplements [1] Regularly [2] Sometimes [3] Rarely [4] Never — 3
c. Fiber supplements [1] Regularly [2] Sometimes [3] Rarely [4] Never — 4

IV. EXERCISE PROFILE

38. Do you engage in physical exercise on a *regular* basis? [1] Yes [2] No *(Skip to item 44)* — 1

39. Do you spend a few minutes doing warm-up activities before engaging in your physical exercises?
[1] Always [2] Sometimes [3] Never — 3

40. Do you spend a few minutes doing cool-down activities after engaging in your physicial exercises?
[1] Always [2] Sometimes [3] Never — 3

Please describe your physical exercise activities:

41. ***Light exercise?*** [1] Yes [2] No *(Skip to item 42)* — 1
Brisk walking
Easy bicycling — ☐ Number of days per week — 3
Easy aerobics
Tennis doubles — ☐☐☐ Minutes per day — 015
Other _____ (Describe)

42. ***Moderate exercise?*** [1] Yes [2] No *(Skip to item 43)* —
Swimming laps
Aerobics — ☐ Number of days per week —
Bicycling
Jogging — ☐☐☐ Minutes per day —
Tennis singles
Other _____ (Describe)

43. ***Vigorous exercise?*** [1] Yes [2] No *(Skip to item 44)* —
Hard bicycling
Running — ☐ Number of days per week —
Intense aerobics
Other _____ (Describe) — ☐☐☐ Minutes per day —

44. Are you taking any prescribed medication (such as "beta blockers") that may limit your ability to increase your heart rate during exercise? [1] Yes [2] No [3] Not sure — 2

If yes, please describe briefly: _____

45. Do you have a physicial condition or handicap that may limit your ability to engage in physical activity? [1] Yes [2] No [3] Not sure — 2

If yes, please describe briefly: _____

V. COPING/STRESS PROFILE

46. Are you presently involved in therapy or counseling? [1] Yes [2] No — 2

47. In general, how satisfied are you with your life? [1] Mostly satisfied [2] Partly satisfied [3] Mostly disappointed [4] Not sure — 2

48. Do your social ties with family and friends provide you with a feeling of support when you have problems? [1] Most of the time [2] Rather often [3] Only sometimes [4] Rarely or never — 2

49. I experience a lot of stress on my job. [1] Very often [2] Rather often [3] Sometimes [4] Rarely or never — 2

50. I experience a lot of stress in my personal life. [1] Very often [2] Rather often [3] Sometimes [4] Rarely or never — 2

51. Have you experienced any of the following in the past six months? Please check all applicable boxes.

a.	Death of spouse	a. ☐
b.	Divorce	b. ☐
c.	Marital separation	c. ☐
d.	Death of close family members	d. ☐
e.	Personal injury or illness	e. ☑
f.	Marriage	f. ☐
g.	Fired at work	g. ☐
h.	Marital reconciliation	h. ☐
i.	Retirement	i. ☐
j.	Change in health of family member	j. ☐
k.	Pregnancy	k. ☐
l.	Sex difficulties	l. ☐
m.	Gain of new family member	m. ☐
n.	Business readjustment	n. ☐
o.	Change to different line of work	o. ☐
p.	Change in number of arguments with spouse	p. ☐
q.	High mortgage	q. ☑
r.	Foreclosure of mortgage or loan	r. ☐
s.	Change in responsibilities at work	s. ☑
t.	Son or daughter leaving home	t. ☑
u.	Trouble with in-laws	u. ☑
v.	Outstanding personal achievement	v. ☑
w.	Spouse begin or stop work	w. ☐
x.	Begin or end school	x. ☐

y.	Change in living conditions	y.
z.	Change in personal habits	z.
aa.	Trouble with boss	aa.
bb.	Change in work hours or conditions	bb.
cc.	Change in residence	cc.
dd.	Change in schools	dd.
ee.	Change in recreation	ee.
ff.	Change in church activities	ff.
gg.	Change in social activities	gg.
hh.	Low mortgage or loan for lesser purchase	hh.
ii.	Change in sleeping habits	ii.
jj.	Change in number of family get-togethers	jj.
kk.	Change in eating habits	kk.
ll.	Vacation	ll.
mm.	Christmas holiday season	mm.
nn.	Minor violations of the law	nn.

52. Please indicate the extent to which the symptoms listed below are *troublesome* to you, as follows:
[1] Extremely [2] Very [3] Moderately [4] Slightly or not at all [5] Does not Apply

Physical symptoms

a. Fatigue
b. Muscular tension
c. Upset stomach
d. Lump in throat
e. Dry mouth
f. Dizziness
g. Pounding of heart
h. Shortness of breath
i. Sleep disturbance

Emotional Symptoms

j. General irritability or depression
k. Persistent unwanted thoughts
l. Urge to cry
m. Fearfulness
n. Self-blame
o. Hopelessness about the future
p. Trouble concentrating

Interpersonal Symptoms

q. Difficulties with co-workers or family members
r. Wanting to withdraw from social situations
s. Outbursts of temper, increased argumentativeness
t. Marital problems, including sexual ones

y.	Change in living conditions	y.
z.	Change in personal habits	z.
aa.	Trouble with boss	aa.
bb.	Change in work hours or conditions	bb.
cc.	Change in residence	cc.
dd.	Change in schools	dd.
ee.	Change in recreation	ee.
ff.	Change in church activities	ff.
gg.	Change in social activities	gg.
hh.	Low mortgage or loan for lesser purchase	hh.
ii.	Change in sleeping habits	ii.
jj.	Change in number of family get-togethers	jj.
kk.	Change in eating habits	kk.
ll.	Vacation	ll.
mm.	Christmas holiday season	mm.
nn.	Minor violations of the law	nn.

52. Please indicate the extent to which the symptoms listed below are *troublesome* to you, as follows:
[1] Extremely [2] Very [3] Moderately [4] Slightly or not at all [5] Does not Apply

Physical symptoms

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b. Muscular tension
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i. Sleep disturbance

Emotional Symptoms

j. General irritability or depression
k. Persistent unwanted thoughts
l. Urge to cry
m. Fearfulness
n. Self-blame
o. Hopelessness about the future
p. Trouble concentrating

Interpersonal Symptoms

q. Difficulties with co-workers or family members
r. Wanting to withdraw from social situations
s. Outbursts of temper, increased argumentativeness
t. Marital problems, including sexual ones

Behavioral Symptoms

u. Deterioration in job performance

v. Development of new personal habits, e.g., nail biting, teeth grinding, throat clearing

w. Problems in making routine decisions

x. Change in appetite

y. Increased use of alcohol

z. Increased smoking

aa. Use of drugs

bb. Lateness in appointment keeping

cc. Absenteeism or lateness on job

53. Do you regularly make time for any of the following?

Time away from work to relax and unwind.	[1] Yes	[2] No
Practice a form of deep relaxation such as:		
Meditation	[1] Yes	[2] No
Progressive muscle relaxation	[1] Yes	[2] No
Deep breathing	[1] Yes	[2] No
Biofeedback	[1] Yes	[2] No
Practice effective time management	[1] Yes	[2] No
Seek out and talk about personal matters with someone you trust	[1] Yes	[2] No
Plan and participate in regular entertainment or engage in pleasurable hobbies	[1] Yes	[2] No
Delegate or ask for assistance in performing tasks which might otherwise seem overwhelming	[1] Yes	[2] No
Eat a balanced diet, including at least *one* hot meal a day	[1] Yes	[2] No
Engage in regular exercise several times a week	[1] Yes	[2] No
Get the amount of sleep which seems sufficient for you	[1] Yes	[2] No
Give and receive affection regularly	[1] Yes	[2] No
Take regular vacations	[1] Yes	[2] No

54. Do you do any of the following?

Practice defensive driving	[1] Yes	[2] No
Pursue routine preventive health care	[1] Yes	[2] No
Have a budget and stick to it	[1] Yes	[2] No
Choose an appropriate time and place to speak openly about your feelings when angry or worried	[1] Yes	[2] No
Let someone else drive if you have consumed alcoholic beverages or are overly fatigued	[1] Yes	[2] No
Carry adequate personal and property insurance	[1] Yes	[2] No

VI. WORKSHOPS

55. Would you be interested in workshops on any of the following topics?

☐ Nutrition ☐ Smoking ☒ Stress ☒ Weight ☐ Substance Abuse

VII. MEDICAL PROFILE

56. Considering your age, how would you describe your overall physical health?
[1] Excellent [2] Good [3] Fair [4] Poor — 3

57. How many days of work have you missed in the past year due to your own illness or injury?
[1] None [2] 1–3 [3] 4–9 [4] 10 or more — 4

58. Has your physician ever said you have chronic bronchitis or emphysema?
[1] Yes [2] No [3] Not sure — 2

59. Do you have diabetes? [1] Yes [2] No [3] Not sure — 2

60. Did your mother, father, sister or brother have diabetes?
[1] Yes [2] No [3] Not sure — 2

61. Did either of your parents suffer a heart attack before age 60?
[1] Yes [2] No [3] Not sure — 3

62. Are you presently taking medication to control high blood pressure?
[1] Yes [2] No [3] Not sure — 2

63. Have you lost more than 10 pounds *without* trying to in the past year?
[1] Yes [2] No [3] Not sure — 2

64. Rectal problems
Have you had: Rectal growth? [1] Yes [2] No [3] Not sure — 2
Rectal bleeding? [1] Yes [2] No [3] Not sure — 2
Annual rectal exam? [1] Yes [2] No [3] Not sure — 1
Annual stool test? [1] Yes [2] No [3] Not sure — 1

VIII. WOMEN'S PROFILE

65. Have you had a hysterectomy? [1] Yes [2] No [3] Not sure — 1

66. How often do you have a Pap smear?
[1] At least once a year [3] More than 3 years apart — 5
[2] At least once every 3 years [4] Never had one [5] Not sure

67. Was your last Pap smear normal? [1] Yes [2] No [3] Not sure — 1

68. Do you have vaginal bleeding at times other than your period?
[1] Yes [2] No [3] Not sure — 2

69. Do you take female hormone (estrogen) pills for birth control or to ease menopausal systems?
[1] Yes [2] No [3] Not sure — 1

70. Did your mother, sister or daughter have breast cancer? [1] Yes [2] No [3] Not sure — 2

71. How often do you examine your breasts for lumps?
[1] Monthly [2] Once every few months [3] Rarely or never — 3

72. When was the last time you had a mammogram?
[1] In past year [2] More than a year ago [3] Never had one — 3

Thank you for participating in the UniHealth Program brought to you by Sinai Fitness.
You have taken an important step in promoting your personal health and well-being!

FOR STAFF USE ONLY!

PHYSICAL AND LABORATORY DATA

1.0 **Fitness Assessment**

Muscular Strength	[1] Below Average	[2] Average	[3] Good	[4] Excellent	2
Flexibility	[1] Below Average	[2] Average	[3] Good	[4] Excellent	2
Aerobic Capacity	[1] Below Average	[2] Average	[3] Good	[4] Excellent	2
Pulmonary Function	[1] Normal	[2] Below Normal			1

1.01 **Resting Blood Pressure**

Systolic Blood Pressure	140	mmHg
Diastolic Blood Pressure	92	mmHg
Resting Heart Rate	[illegible]	BPM

1.02 **Body Composition**

Height	120	inches
Weight	[illegible]	pounds
Percent body fat	24	percent

1.03 **Muscular Strength**

Chest press	70	pounds
Adjusted by body weight	[illegible]	%
Leg press	150	pounds
Adjusted by body weight	[illegible]	%

1.04 **Flexibility**

Sit and Reach	2	inches

1.05 **Aerobic Capacity/Bicycle Test**

Aerobic Capacity	[illegible]	ml/kg/min

1.06 **Heart Rate Information**

Target Heart Rate	144	(+/- 4) BPM
Program intensity	[illegible]	% of H.R. Max

1.07 **Laboratory Results**

Total Cholesterol	210	mg/dl
HDL Cholesterol	45	mg/dl

Appendix B

Health Profile and Prescription Form for Individuals

UniHealth

1

Dear Friend,

Congratulations on taking an important first step to promote your personal health by participating in the UniHealth Program!

Our health professionals have prepared this Health Profile & Prescription based on your responses to the Health Risk Assessment questionaire. Much useful advice concerning your health is offered to you here, but please remember that regular visits to your own physician are most important.

This document summarizes your health profile and prescribes specific actions which you can take to feel better and live longer.

PART 1 describes YOUR OVERALL PHYSICAL CONDITION and recommends behavior changes to help you improve it (pages 2-5).

PART 2 deals with the importance of YOUR NUTRITIONAL STATUS and suggests dietary changes which can greatly improve the quality of your life (pages 6-9).

PART 3 addresses FITNESS AND YOUR HEALTH and makes a number of specific recommendations on physical activity and exercise (pages 10-12).

PART 4 discusses STRESS AND YOUR HEALTH and suggests specific actions which you can take to reduce the effect of stress on your well-being (pages 13-14).

PART 5 deals with FEMALE HEALTH PROBLEMS that women should not ignore (page 15).

PART 6 summarizes PERSONAL HABITS AND YOUR HEALTH. It shows how diet, exercise and personal habits act together to promote or damage health. An understanding of these relationships will point you in the direction of reducing your health risks through appropriate modifications of your diet, fitness and behavior (pages 16-18).

PART 7 is a summary UNIHEALTH'S RECOMMENDATIONS for behavioral changes which are most likely to benefit your future health (page 18).

To your good health,

UniHealth Staff

UniHealth

PART 1: YOUR OVERALL PHYSICAL CONDITION

HEALTH RISK

The concept of health risk has to do with the likelihood of your becoming ill or dying. If your risk of a particular disease is high, you have a greater chance of developing that disease or dying from it than other people. We will show you how to reduce your health risks by changing your diet, exercise program or health behavior.

The information on health risks in this report is based on mortality statistics and studies comparing people with and without disease. Because risk factors affect people in different ways, the results of these studies apply to you only in a general way. However, since they offer the best available estimates of health risks, risk factors should be seriously considered whenever you make decisions about your health habits. UniHealth's recommendations to you are based on risk factors which can be reversed or controlled by changing your personal health behavior.

HEALTH AGE

People of the same age are not equally healthy. Some have a "health age" which is younger than their actual age. Others are biologically older than their actual age. Estimating "health age" is a way of judging how risk factors may affect your health. Heredity, diet and personal habits play important roles in determining "health age". Of course, you can't change heredity, but you can change health behaviors under your control.

Your age is approximately 39 years
Your "health age" is 41.6 years

By adopting the recommendations in this report, you can reduce your "health age" to as little as 38.5 years

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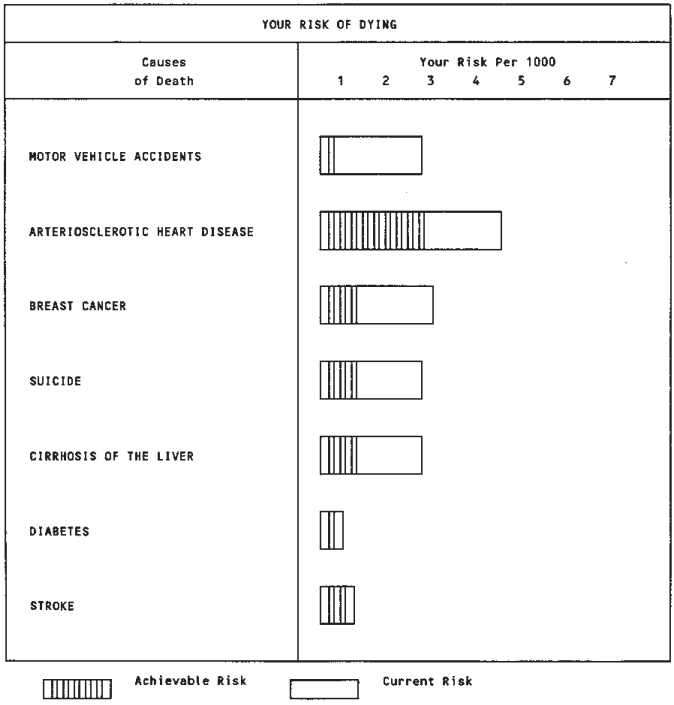
RISK OF DYING

UniHealth has calculated your risk of dying over the next ten years from the leading health risks for persons of your age, race and sex. In the table below, you will find a list of leading causes of death for WHITE FEMALES OF YOUR AGE. To the right of each cause is a bar showing your current risk of death from the cause and the lower risk achievable if you modify your health behavior in the recommended manner. For example, your current risk of death from MOTOR VEHICLE ACCIDENTS may be reduced from 2.59 per thousand to approximately 0.81 per thousand by adopting the health prescriptions suggested in this report.



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GOOD HEALTH HABITS

At the present time, your good health habits, which promote your health and reduce your health risks, should be maintained. These include:

Not smoking or chewing tobacco
Getting regular dental checkups
Having stool test for blood regularly

CURRENT HEALTH RISKS

At present, you have a number of health risks requiring attention. These include:

Cholesterol level
High blood pressure
Paps test not regularly done
Seat belts not regularly used
Medication intake may be too high
Alcohol consumption may be too high
Breast self-exam not regularly done
Diet needs improvement as recommended

LABORATORY DATA AND OTHER MEASUREMENTS

A table summarizing your laboratory and physical examination findings is presented below. You should discuss the findings with your physician.

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YOUR LABORATORY DATA AND MEASUREMENTS

WHITE FEMALE, Age 39

	Your Value	Ideal Range	Your need to improve
I: Blood Pressure			
Systolic	144 mmHg	Less than 120	**
Diastolic	90 mmHg	Less than 80	**
II: Blood cholesterol			
Total Cholesterol (TC)	240 mg/dl	Less than 180	***
HDL Cholesterol	45 mg/dl	More than 60	**
TC/HDL Ratio	5.333	Less than 3	**
III: Body Measurements			
Height	69 inches		
Weight	180 pounds	130 - 148	**
Body Fat (%)	34%	15 - 24%	**
IV: Muscular Strength			
Upper body (chest press)	70 lbs.		
% body weight	38 %	50% of body weight	*
Lower body (leg press)	150 lbs.		
% body weight	83 %	100% of body weight	*
V: Flexibility			
Sit and reach	2 inches	5 inches or more	*
VI: Aerobic Capacity	30 ml/kg/min	Over 33 ml/kg/min	**
VII: Pulmonary Function	Normal	Normal	
VIII: Heart Rate			
Resting Rate	78 bpm	60 - 75 bpm	**
Training Rate	129-160 bpm	50-80% of Max. H.R.	

*** Substantial change needed
** Some change needed
* Little change needed

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PART 2: YOUR NUTRITIONAL STATUS

DIET AND HEALTH

The kinds and amounts of foods that you eat are probably the single most important habit affecting your health. Although vitamin and mineral deficiencies used to be a major concern (and still are in other countries), dietary excesses are the major concern in the United States today. The four most serious dietary excesses include: total fat (saturated and unsaturated); saturated fat; cholesterol; and salt.

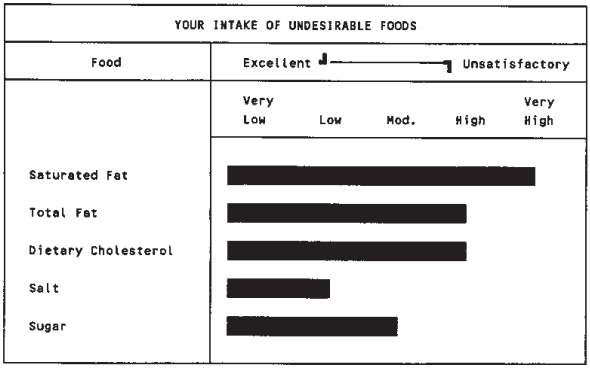
TOTAL FAT, from both animals and vegetables, may increase your risk of breast and colon cancer, two leading causes of death from cancer. Diets containing excess fat are also more likely to cause obesity because fats contain twice as many calories for a given weight as sugar, starch or protein.

SATURATED FAT, mainly from red meats, dairy products and coconut oil, may increase your blood cholesterol and thus increase your risk of arteriosclerosis, circulatory problems, heart attacks and strokes. The same problems may arise from excessive dietary intake of cholesterol, found primarily in egg yolks and organ meats.

SALT, which we tend to eat in great excess, increases your chance of developing high blood pressure, and possibly other serious conditions.

SUGAR is also consumed in excess by many of us. This contributes to obesity, dental problems and diabetes. However, because sugar has fewer calories than an equal weight of fat, it is less likely to be a serious cause of disease for you than excess salt or fat.

How does your diet compare to others' in the intake of these relatively undesirable types of food? Examine the chart below.



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UniHealth Recommends:

Lower your blood cholesterol to reduce your risk of heart attack. To do this, you should lose excess weight and reduce the amount of saturated fat and cholesterol in your diet.

Reduce your weight to aproximately 148 lbs. This is especially important because of your high total blood cholesterol level (240 mg/dl), your borderline blood pressure level (144/ 90 mmHg) and your low HDL cholesterol level (45 mg/dl). You can lose weight by increasing your physical activity and reducing your dietary intake of fat, both saturated and unsaturated.

Reduce your dietary intake of total fat, saturated fat and cholesterol by changing your eating habits, as follows:

1) Eat poultry, fish, lean cuts of veal, or seafood in place of red meat whenever possible.

2) Choose lean cuts of any red meat that you do eat.

3) Trim visible fat from meat before cooking.

4) Broil meat rather than fry it: in general, choose cooking methods which allow fat to run off.

5) Remove skin from poultry before cooking.

6) Eliminate organ meats such as liver, kidney and heart.

7) Eat no more than 2 egg yolks each week. (Egg whites are fully acceptable and a good source of protein.)

8) Use tub margarine in place of butter, ~~but also try to reduce your consumption of these substances~~.

Your blood pressure is 144/ 90 mmHg, which indicates borderline hypertension. Change your diet as follows:

1) Eliminate high salt processed foods such as canned soups or luncheon meats.

2) Do not add salt to your food at meals.

3) Use a minimum of salt, or no salt at all, in cooking.

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OTHER NECESSARY NUTRIENTS

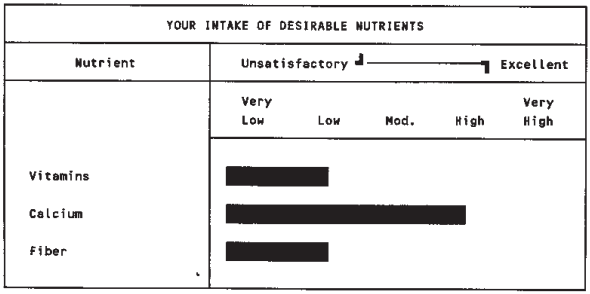
Although most Americans today are unlikely to suffer from major deficiencies of vitamins, protein and calories, you may be at risk of some less obvious dietary deficiencies which have come to light in recent years.

Vitamins and trace elements appear to be useful in retarding, or perhaps preventing, some forms of cancer. Beta-carotene (the orange coloring matter in carrots and sweet potatoes) is converted by the body into VITAMIN A. It seems to help prevent the growth of several types of cancer. VITAMINS C and E, as well as substances contained in cruciferous vegetables (the cabbage family), may also be protective against cancer.

Many women do not consume enough CALCIUM early in their life to prevent the development of brittle bones (osteoporosis) in later years. Men can also develop osteoporosis, although it is much less common among them, except in very old age.

FIBER (the indigestible part of your diet which adds bulk to your stool) is often deficient in persons who regularly eat white bread, sugar and other highly refined foods rather than bran, whole grains and whole fruits. Fiber may also help prevent colon cancer and slow the absorption of dietary cholesterol.

How do you compare to others in your intake of these highly desirable types of food? Examine the chart below.



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For your intake of vitamins, trace elements and fiber, UniHealth recommends:

VITAMINS

Your diet appears to provide you with an adequate amount of vitamins. Be sure to maintain this good eating habit and include foods which may lower your risk of certain cancers:

1) Cruciferous vegetables (cabbage family)

2) Foods rich in Vitamin E (dark green, leafy vegetables)

3) Foods rich in Vitamin C (citrus, strawberries, green and red peppers, and potatoes)

4) Foods rich in beta-carotene (carrots, apricots, peaches, spinach, melon and sweet potatoes).

CALCIUM

Your diet appears to provide you with an adequate amount of calcium.

FIBER

Your diet appears to contain less than the desirable amount of fiber. To reduce your risk of cancer and certain other digestive diseases, eat cereal made with bran or add bran fiber to other foods and increase your daily consumption of fruits and vegetables, particularly including legumes such as split peas and beans.

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PART 3: FITNESS AND YOUR HEALTH

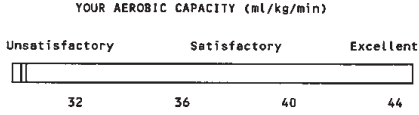
EXERCISE

Regular physical exercise gives you many benefits, including improved fitness, weight control and stress reduction. It reduces your risk of heart attack by lowering blood cholesterol and blood pressure, especially when you also lose excess weight at the same time. Exercise also helps stabilize your blood sugar level and increases your bone mass, which may prevent osteoporosis.

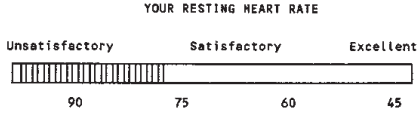
Fitness reflects your body's capacity to do work, such as walking or running. It is often measured in terms of "aerobic capacity" which permits the fitness levels of different people to be compared. Fitness can also be measured in terms of the resting heart rate.

YOUR FITNESS

Your estimated aerobic capacity, as shown in the graph below, is 30 ml per kg per minute. A satisfactory level for someone your age, sex and race is 36 ml per kg per minute.



Your resting heart rate, as shown in the graph below, is 78 beats per minute. A satisfactory resting heart rate for someone of your age, sex and race is between 60 and 75 beats per minute. Resting heart rates as low as 40 beats per minute are also not uncommon, especially among people who exercise regularly. In fact, the lower your resting heart rate, the better your fitness.



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IMPROVING YOUR FITNESS

The only way to improve your physical fitness is through regular aerobic exercise. "Aerobic" exercise includes any kind of sustained, rhythmic activity that involves the use of large muscles such as those in your arms and legs. Examples of aerobic exercise are brisk walking, jogging, hiking, cycling, swimming, and active sports such as basketball and tennis.

For you to achieve the benefits of physical fitness, you must exercise at least three times each week for a minimum of 20 minutes at a time. You must also maintain an intensity of exercise that causes you to be slightly out of breath and that increases your heart rate to the "training level."

You may measure your heart rate by counting your pulse at the wrist for 10 seconds immediately after you stop exercising. Multiply the number by six to get your heart rate.

The "training level" of your exercise heart rate, as shown in the graph below, is in the range between 129 to 160 beats per minute. On this basis, UniHealth prescribes an exercise heart rate target for you of 144 beats per minute.

YOUR EXERCISE HEART RATE TARGET

Your current level of aerobic exercise is INADEQUATE to promote your physical fitness. To improve your fitness, UniHealth recommends:

BEGIN TO EXERCISE ON REGULAR BASIS. Choose a moderately vigorous activity that you enjoy and do the following:

1) Perform the activity 3 times per week, preferably every other day.

2) Each exercise session should be at least 20 minutes long. After one month, gradually increase the length of the session to at least 30 minutes.

3) When you exercise, try to keep your heart rate in the prescribed training range, i.e. between 129 and 160 beats per minute. For optimal fitness benefits, exercise at your target heart rate of 144 beats per minute.

CAUTION: Warm up for at least five minutes before you begin to exercise and cool down for at least five minutes after you finish. Appropriate warm-up and cool-down activities consist of low-intensity exercises such as walking, arm swinging, light stretching or cycling in low gear. These activities will protect you against injury and prepare your heart to recover from the vigorous exercise that you have engaged in.

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PART 4: STRESS AND YOUR HEALTH

STRESS

Stress is an inescapable fact of life which contributes both to the joys and sorrows of living. Any change in our routine, even changes that are positive, may introduce stress in our lives. Minor annoyances and the daily pressures of our business and personal lives can also do this. Whatever its cause, stress requires adjustment by the individual, if it is to be controlled.

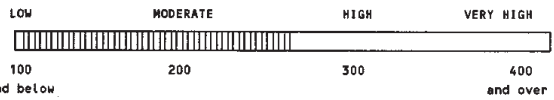
MEASURING STRESS

Stress, and the ability to deal with it, is measured in various ways. For example, the amount of stress caused by life events to which we must adjust, varies from person to person. In addition, many life events lie beyond anyone's personal control, yet these may be more or less stressful to different people when they occur.

Studies involving thousands of individuals have made it possible to estimate the degree of stressfulness of specific life events and to calculate overall stress scores for an individual's life events. The overall stress scores range between 100 and 500 which make it possible to identify those individuals who are at risk of becoming physically or emotionally ill from the stresses in their lives. As an example, 80 percent of people with scores above 300 can be expected to suffer a serious illness within two years, as compared to only 33 percent of persons scoring between 150 and 250.

UniHealth has measured your life events and scored them on a life event scale as shown below.

YOUR LIFE EVENTS SCALE



Stress is expressed by many physical, emotional, interpersonal and behavioral reactions or symptoms. In your Health Risk Assessment, you reported that you are currently experiencing 10 reactions which be symptomatic of stress out of a possible 29 and that 2 of these are quite troublesome to you. You also indicated that you are experiencing stress in your work and personal life.

COPING SKILLS

There are many ways to cope effectively with daily stresses in our lives. While many of these are learned in childhood and applied in later life, other coping skills can be learned at any time and used to advantage. A combined score of 13 or more in the coping scale indicates successful coping with current stress and the ability to adapt to new and unanticipated demands. On the other hand, a score of eight or less on the coping scale suggests that the individual needs to further develop his or her coping skills. UniHealth has determined that your score on the General Coping Scale is 9 .

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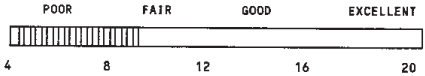
YOUR GENERAL COPING SCALE



To deal with your particular stresses, UniHealth recommends:

Your degree of satisfaction with life and close relationships with family and friends indicate relatively low stress levels, effective coping skills and good mental health. You have reported that, despite high stress levels and lack of close personal relationships, you are generally satisfied with your life.

Certain events or situations can produce stress, depending on how much they disturb our daily routine or life styles. You have experienced many such potentially stressful life events, including 1 major one(s), during the past six months, which required a substantial adjustment in your life. In the section below, UniHealth examines your reactions to stress, and suggests ways to deal with them.

Stress can produce a variety of symptoms -- physical, behavioral, emotional or interpersonal -- which can be very upsetting to those who experience them. In addition, they often make if difficult to function well at work or with your family and friends. You report that you are currently experiencing 10 of these symptoms (with 2 being very troublesome to you). Joining a stress management program could be effective in helping you to reduce these stress reactions. If your physical symptoms of fatigue, muscular tension, pounding of heart, and sleep disturbance persist, you should discuss them with your doctor.

You can also manage much of the stress in your life through the routine practice of coping techniques. Some of these techniques are aimed at reducing stress; others can help you achieve a balance between work and play. You have reported to UniHealth that you regularly practice 9 coping techniques. This suggests that you are enjoying a degree of success in dealing with the stresses of life. However, you might wish to add a few other coping techniques such as deep relaxation practices.

Certain other techniques can also help prevent stressful reactions or protect you from being overwhelmed by them. You report practicing a few such techniques. You may find it helpful to add the following:

Manage your time more efficiently
Emphasize the prevention of bad habits
Develop a reasonable budget and stick to it
Express your needs and feelings more effectively
Driving defensively, especially when you have been drinking or are tired

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PART 5: FEMALE HEALTH PROBLEMS

You report that you have had a hysterectomy. If this involved an abdominal operation, it means that you need not continue to have Pap smears or be concerned about cervical or uterine cancer. However, you should continue to see your doctor on a regular basis to prevent other gynecological problems and to undergo regular, professional breast examination.

You report taking estrogen (hormone) pills. This medication should be carefully monitored by your physician, because it can sometimes cause abnormal bleeding and other problems.

You also report that you do not regularly examine your breasts for lumps. Breast self-examination is an effective way to detect lumps which might be cancerous or could become cancerous. There is a high cure rate for breast cancer, especially when it is detected and treated early. Therefore, practice breast self-examination to reduce your risk. A mammogram is an x-ray test which can detect lumps before they can even be felt. Women with a family history of breast cancer, or who over 50, should arrange for mammograms on a regular basis to reduce their risk breast cancer.

Be sure to see your doctor regularly to monitor your estrogen medication. If abnormal bleeding or other problems occur, visit your doctor promptly.

Practice breast self-examination monthly, and make sure it is performed annually by a doctor or nurse when you have a medical check-up. If you are not certain how to do breast self-examination, contact your physician.

Have your first mammogram no later than age 50. A "baseline" mammogram close to age 40 is a good idea, recommended by many physicians.

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PART 6: PERSONAL HABITS AND YOUR HEALTH

The personal habits and behaviors that you adopt can promote your health or damage it. For example, proper exercise and diet improve your fitness, while smoking and excessive use of alcohol or drugs increase your risk of serious disease. UniHealth summarizes its findings on how effectively you are dealing with smoking, alcohol and drugs in the paragraphs below.

SMOKING

As a former smoker, you must be aware that smoking increases your risk of many diseases. If you begin to smoke again, your risks of these diseases will increase. Unihealth reminds you to make every effort NOT to resume smoking. Keep in mind that many people who have failed to stop smoking, try again and and eventually suceed.

ALCOHOL

You report drinking an amount of alcohol that may possibly be a cause of concern. This puts you at risk of a variety of problems such as automobile accidents, heart disease, and alcoholism.

UniHealth recommends:

> Reduce your level of alcohol consumption or stop drinking alcohol entirely. You may find it helpful to seek professional assistance to accomplish this.

DRUGS

You report sometimes using drugs to improve your mood, help you sleep, pep you up or lose weight. This may indicate that you are having trouble finding more healthful ways to deal with these stressful situations.

UniHealth recommends:

> Explore alternative ways to improve your mood, help you sleep, pep you up or lose weight. Use of medications for this purpose on a short-term basis is not likely to be harmful. However, if you use them regularly, you may wish to consult with your physician.

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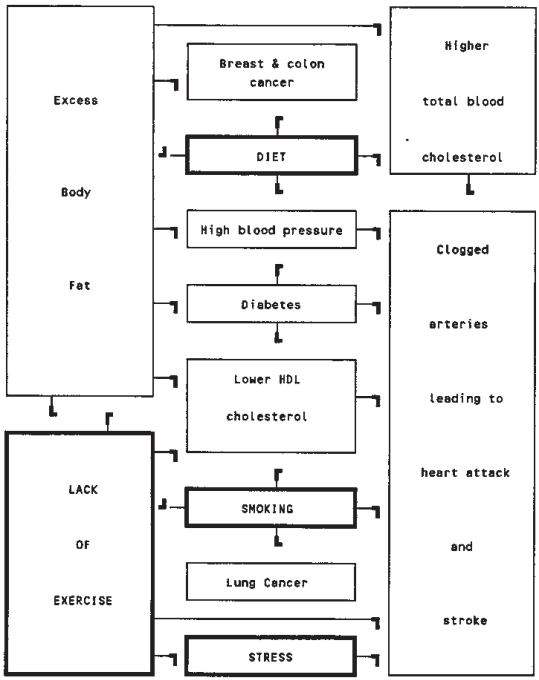
The diagram below illustrates some of the important relationships between personal health habits (e.g. diet, exercise), body measurements and functions (e.g. body fat, blood pressure, blood cholesterol) and disease (e. g. heart attack, stroke and cancer). More than half of all deaths in the United States are attributable, at least in part, to one or another bad health habit. This means that more than half of all deaths can be prevented, or at least postponed, by changes in personal health habits.

Notice in the diagram below that one habit, smoking, may have a number of adverse effects on your health: lung cancer, heart attack and low HDL cholesterol, for example. Notice also that one disease, atherosclerosis (clogged arteries) may be caused by a number of different health habits: diet, lack of exercise, smoking and stress, acting separately or together. Use the diagram to help you understand the different ways in which your own personal health habits, body measurements and laboratory data can act together to affect your health. An understanding of this will help you determine the ways in which you may reduce your health risks by appropriate changes in your health behavior.



LEGEND: Habits under your own direct control (at least to some extent) are shown in the bold boxes, e.g. DIET, SMOKING. The effects of these habits are shown in the thin lined boxes, e.g. high blood pressure, heart attack.

Appendix C

Corporate Health Profile and Prescription Form

Executive Summary

I. Introduction

The Value of Health Promotion in the Corporate Setting
What is "Health Risk"?
Purpose of the Corporate Report

II. Program Description and Timetable

III. Participant Profiles

IV. General findings

A. Health Age of the Organization
B. Leading Risks
C. Coronary Risk Profile
D. Stroke Risk Profile
E. Cancer Risk Profile
F. Nutrition
G. Exercise/Weight Control
H. Coping/Stress
I. Tobacco
J. Alcohol
K. Medications
L. Medical Profile/Family History
M. Dental
N. Automobile
O. Women's profile
P. Conclusion and Recommendations

Q. Health Needs and Likelihood of Change Among
R. Intervention Recommendations
S. Conclusions and Recommendations

V. Appendices

VI. Specific Findings of Importance

I. INTRODUCTION

THE VALUE OF HEALTH PROMOTION IN THE CORPORATE SETTING

The Surgeon General of the United States pointed out in the book "*Healthy People*" that *50%* of all premature deaths (before age 65) *are preventable*. This is because they are caused by "lifestyle diseases"—those for which a major cause is personal *behavior* that is detrimental to health. This 50% figure can be looked at in another way, in combination with the other factors that contribute to early death:

50% are due to behavior detrimental to health
20% are due to environmental causes
20% are due to hereditary causes
10% are due to lack of adequate medical care

"Serious diseases are preventable—or at least postponable". This is the way Roger B. Smith, Chair and CEO of General Motors Corp., described the impetus behind wellness programs, which "promote behavioral change that eliminate lifestyle diseases". The Health Insurance Association of America views health promotion as "an integral part of management strategy to trim health care costs".

Many of the companies, which have implemented health promotion programs in the recent past, are beginning to estimate with some precision the bottom-line results:

- AT&T Communications in New Jersey estimates $2.6 million *net* annual savings, derived from costs of $2.2 million and savings of $4.8 million.

- Blue Cross/Blue Shield of Indiana reports $2.5 returned for every $1.0 spent on health promotion and $1.6 million total 4-year savings (1978–1982) based on reduced employee insurance claims alone.

Other beneficial effects of health promotion programs include reductions in absenteeism, turnover, accidents and lost time, and improvements in morale, recruitment and productivity. Health promotion is an affirmative, proactive approach, which can involve all employees (and possibly dependents). Its implementation has a positive impact on corporate culture when employees are encouraged to share responsibility for a matter that affects them closely, namely their health.

WHAT IS "HEALTH RISK"?

The concept of risk in relation to health deals with probabilities of becoming ill or of dying. A working population or an individual, with elevated risk factors has a *greater chance* (but *not* a certainty) of becoming ill or of dying. This probability can be reduced by controlling those factors that contribute to the increased risk.

The predictions of risk used in this report are based on mortality statistics and on major epidemiological studies on the causes of death and development of disease or disability. These studies examined the relationships between *health history, health habits, and subsequent illness and death* over a 10-year period in large groups of Americans, categorized by age, race and sex. The factors most clearly associated with later development of disease and death are called *risk factors*. In this report, Uni Health recommendations are based upon those risk factors that can be reversed or controlled through changes in personal health behavior.

Risk factors have different effects on different people; thus, these study results apply only in a *general* way to a given individual. They definitely apply to groups of people, however, from similar populations. In sum, they represent the best available estimates on *health risks*, and provide useful information with which an organization can make intelligent decisions about the future health and health habits of its employees.

PURPOSE OF THE CORPORATE REPORT

This report is designed to serve as a "health audit" for your company. The audit will allow you to assess the current strengths and weaknesses of your organization's health risk profile, to share the results as appropriate with employees, who will have completed their own personal "health audits", and to make decisions as to how you may wish to enhance the strengths and repair the weaknesses of your company's overall health profile. The corporate report will also permit you to examine the relationship between employees' *health* status and your expenses for *medical care*, as well as project trends in the near future.

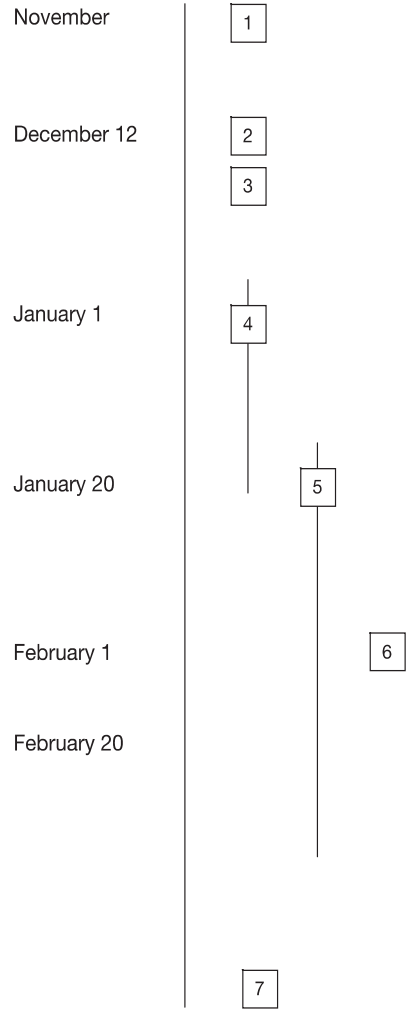
In addition, if your firm tracks, or intends to track, absenteeism, accidents, employee turnover or other measures of productivity, you will be able to relate the trends in these areas to the trends in health status reflected in your Corporate Health Risk Profiles.

II. PROGRAM DESCRIPTION AND TIMETABLE

The UniHealth Health Risk Assessment (HRA) program is part of the overall health promotion program offered by Sinai Fitness on a contractual basis with Goodnuff Corporation. All employees were invited to participate Program description and participant enrollment forms were provided in brochures in the December 12 paychecks, and by an article in the December house organ, GOODNUFF NEWS.

For all participants in the UniHealth program, the Human Resources Department's Wellness Coordinator will schedule appointments with staff members from Sinai Fitness on company time. Sinai Fitness staff members performed fitness and physiological measurements, drew a blood sample for laboratory analysis and had each individual complete the UniHealth questionnaire. Each appointment took 40-45 minutes.

Time Line of Start-Up Events
HEALTH PROMOTION PROGRAM
Goodnuff Corporation



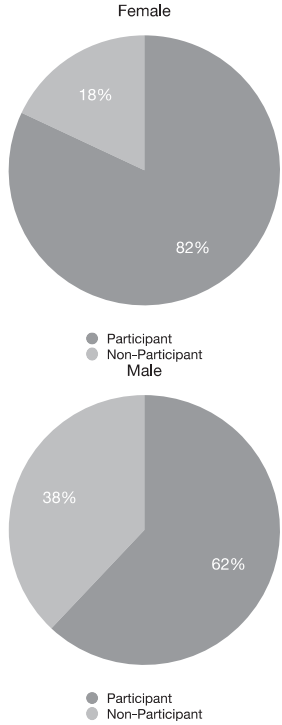
1. Corporate discussion about health promotion program held with Sinai Fitness; decision to implement.
2. Program description and forms are included in paychecks
3. Article appears in Goodnuff News describing health promotion program.
4. Participating employees complete health risk assessment, have physical and laboratory measurement performed. Sessions are held in January.
5. Participating employees return to receive an discuss results of assessment, make plans for acting upon results. Sessions scheduled for late January through mid-February.
6. Top management receives corporate report summarizing results.
7. Implementation of initial segments (exercise and weight control); final planning for full implementation of all segments, based on results of initial questionnaire.

III. PARTICIPANT PROFILES

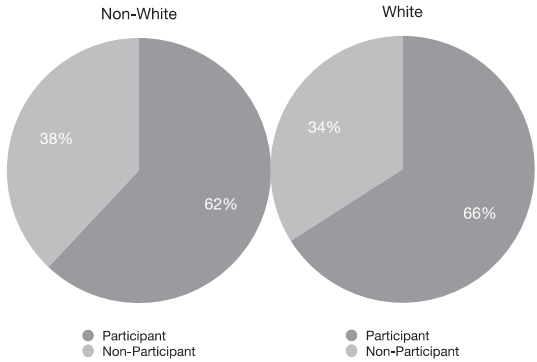
An appraisal of the health risk status of Goodnuff Corporation employees was performed during January, 1987. Of the 1,000 employees eligible to participate, 669 (67%) volunteered and 652 (65%) completed the program. The participants had an average age of 40 years, where 60% were female and 80% white. Thus, they were younger and included more females than the company as a whole.

The analysis below includes data provided by your personnel office. Your employee population was studied in terms of income level, as well as the demographic factors of age, race, sex and tenure with your company. This allows you to analyze the overall health risks among various segments of your participating employees, to compare this to your total population and thus to analyze your organization's needs for further prevention activities. This may be done according to health problem areas as well as economic factors, considering such issues as which employees are most costly to replace, as reflected by income level and longevity with your company.

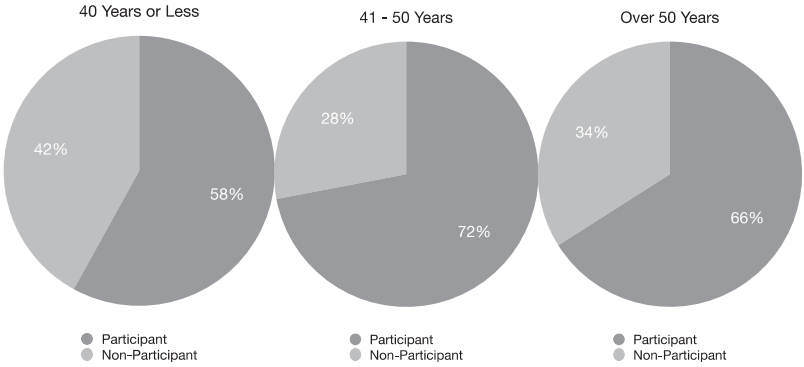
RATES BY SEX



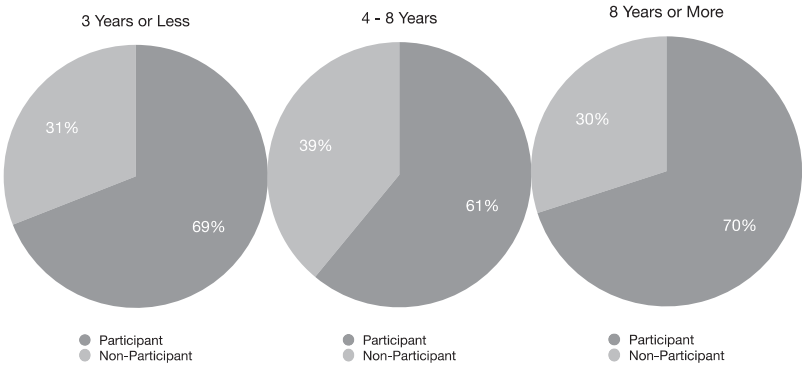
RATES BY RACE



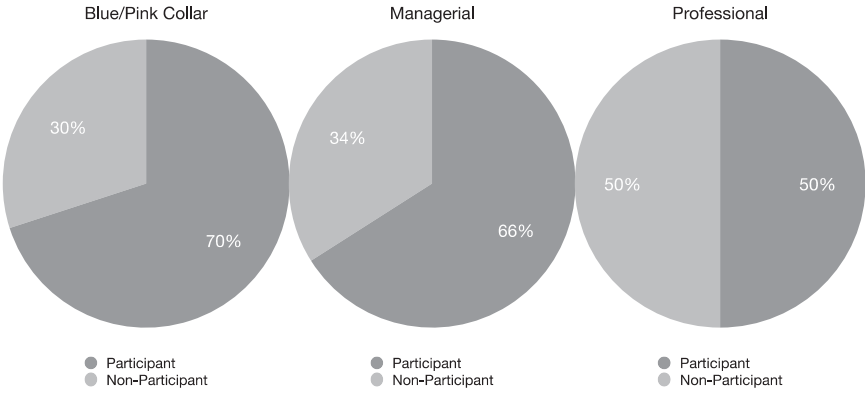
RATES BY AGE



RATES BY LENGTH OF EMPLOYMENT



RATES BY EMPLOYMENT LEVEL



IV. GENERAL FINDINGS

The majority of participants (89%) reported that they are in good or excellent health. This is a very positive finding, and it may accurately reflect their current status. At the same time, however, *73%* were found to have a pattern of health behaviors or modifiable health conditions, which placed them at *increased risk* for developing, and possibly dying from, certain serious disease during the next ten years.

A. HEALTH AGE OF THE ORGANIZATION

What is "health age"? People of the same age are not equally healthy. Some have a "health age" younger than their actual age, while others are biologically older than their actual age. An estimated "health age" provides a way to interpret how the various risk factors may affect one's health. Heredity, diet and personal habits play important roles in determining health age. The figures below show the actual age, then the health age and the average achievable age for employees who participated in the HRA program. The achievable age is that which can be achieved by influencing the risk factors over which an individual has control.

Average	Total (n=652)	Men (n=261)	Women (n=391)
Actual age	40.4 years	39.0 years	41.3 years
Health age	42.6	41.8	43.4
Achievable age	38.1	38.0	38.2

Potential gain in health years 2.3 3.8 5.2

B. LEADING RISKS

Below are the 5 causes of death for which the men and women in your organization are at highest risk, based upon their responses on the health risk assessment, compared to others of the same age, race and sex.

Rank	Risk (Men)	No. persons at high risk	% persons at high risk
1.	Motor vehicle accidents	82	31.3
2.	Arteriosclerotic heart disease	78	30.0
3.	Stroke	58	22.1
4.	Lung cancer	38	14.7
5.	Cirrhosis of the liver	26	9.8
	Risk (Women)		
1.	Arteriosclerotic heart disease	70	17.9
2.	Stroke	63	16.1
3.	Motor vehicle accidents	47	12.0
4.	Lung cancer	42	10.8
5.	Breast Cancer	16	6.1

The *three diseases* for which your employees, both men and women combined, had the highest risk are:

Heart Disease – 30% are at increased risk
Stroke – 19% are at increased risk
Cancer – 15% are at increased risk

Note also that 70% indicated they feel under excessive stress at home and/or work.

A more detailed look into each of the three disease areas will provide additional insights and make it easier to reach decisions about how to design solutions to each of these problem areas.

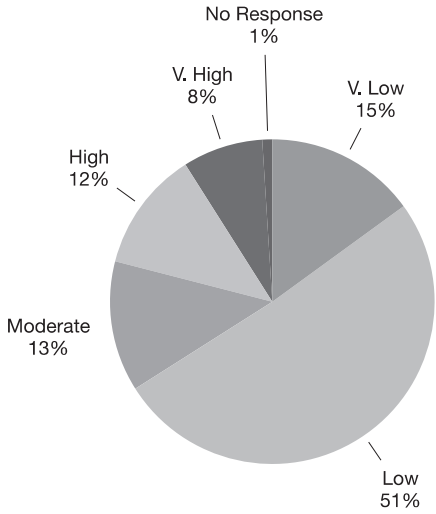
C. CORONARY RISK PROFILE

An assessment of the risk of death from heart attack has been made for each of your employees who participated in the Health Risk Appraisal. This assessment is based on those risk factors for heart attack, which are to some extent under the control of the individual, e.g., blood pressure, blood cholesterol, cigarette smoking, physical activity and body weight. A score of zero is optimal. Risk increases as the score increases. Some of the same risk factors, which increase the risk of heart attack, also increase the risk of other types of circulatory disease and the most common forms of cancer. All individuals in the categories of moderate, high and very high risk would be likely to benefit from a risk reduction program designed to address the various factors contributing to these risk levels.

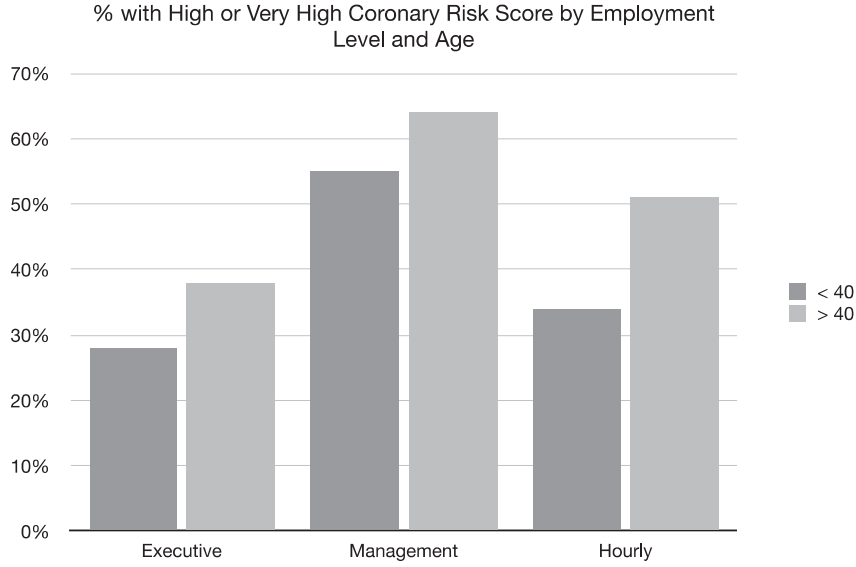
The following table and pie chart depict the percentages of your employees who are at risk of having a heart attack.

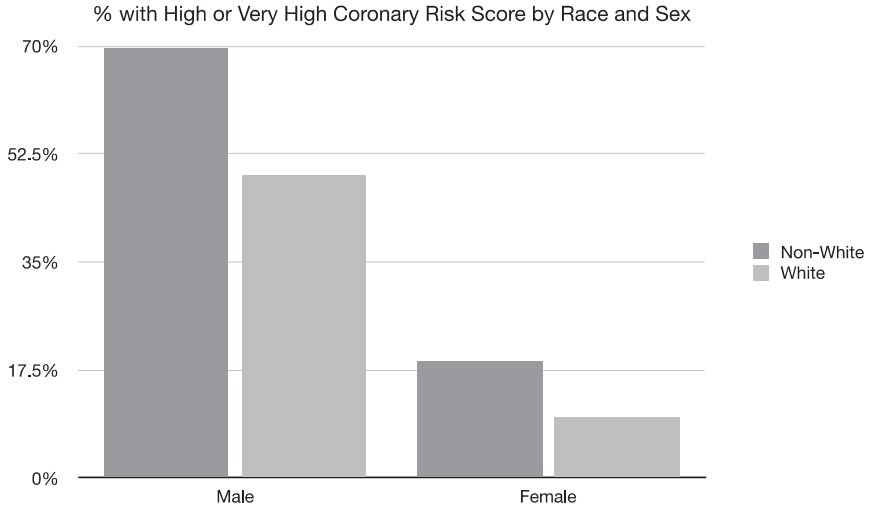
PERCENTAGES AT RISK OF HEART ATTACK

No. of Employees	Risk factor	Score	% of Employees
Very low	(0-100)	75	15
Low	(101-20)	255	51
Moderate	(201-40)	65	13
High	(401-500)	60	12
Very high	(over 500)	40	8
No response		15	1



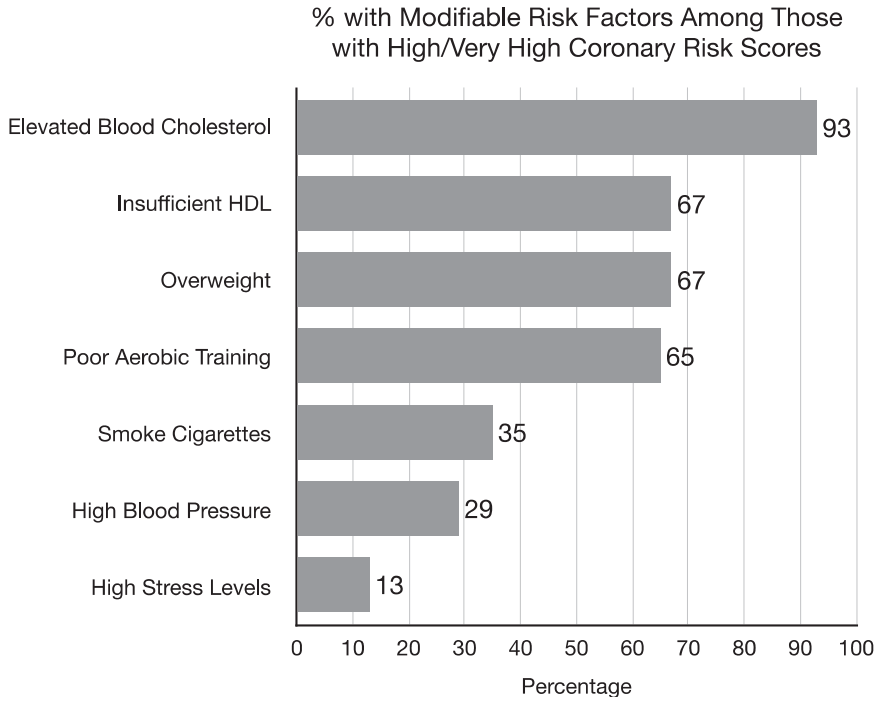
The following graphs show employee groups at highest risk of having heart attack.



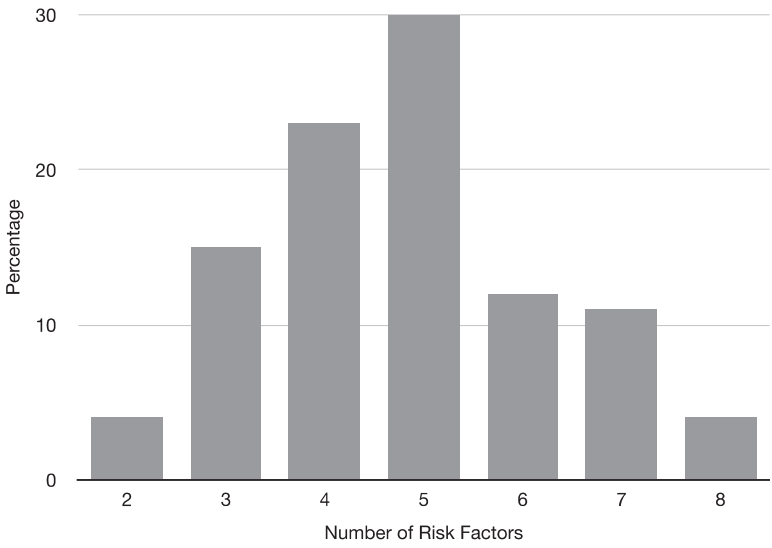


DATA RELATING TO MODIFIABLE RISK FACTORS

Among the 100 employees with high or very high coronary risk scores, the modifiable risk factors were as follows.

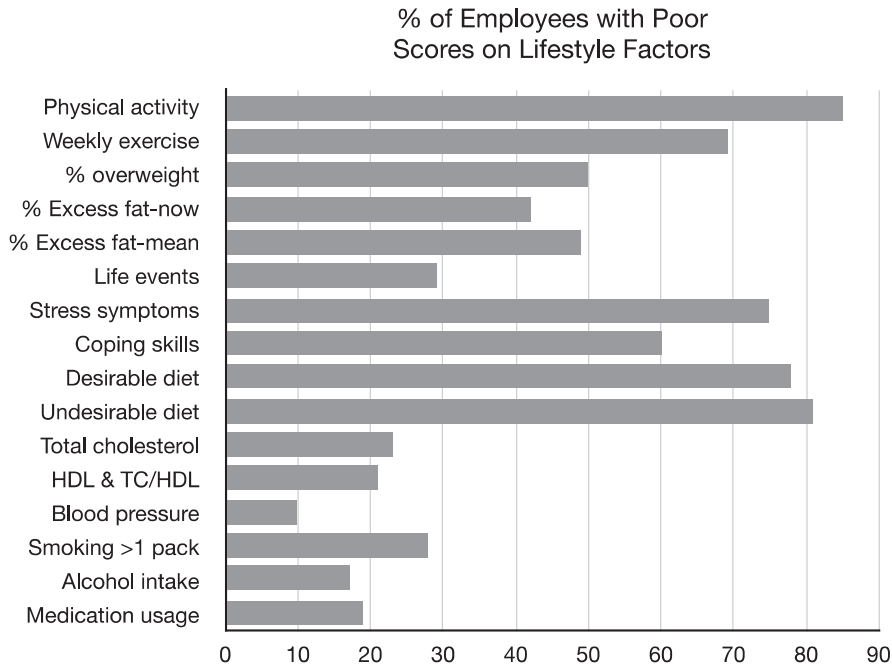


Individuals with high or very high coronary risk scores have more than one risk factor, as shown in the graph below. This fact compounds their increased risk of heart attack and stroke. At the same time, however, having several risk factors provides such individuals with several opportunities to reduce their risk level.



# of Risk factors Among People with High/Very High Coronary Risk Factor

How can you determine where health behavior changes could be most beneficial? The following graph shows the percentage of employees whose response indicated a low level of attainment on lifestyle factors identified by the UniHealth Program. High percentages of employees with low scores (longest bars) clearly point out the most desirable lifestyle changes.



V. CONCLUSIONS AND RECOMMENDATIONS

A. HEALTH NEEDS AND LIKELIHOOD OF HEALTH BEHAVIOR CHANGES

The chart on the following pages shows the percentages of your employees who have unmet health and lifestyle-related needs, and those who desire assistance in improving selected aspects of their health and lifestyle. It then combines these figures to show what proportion of employees with health needs desire assistance, and what proportion wish to improve their lives in certain respects, even though problems are not present at this time.

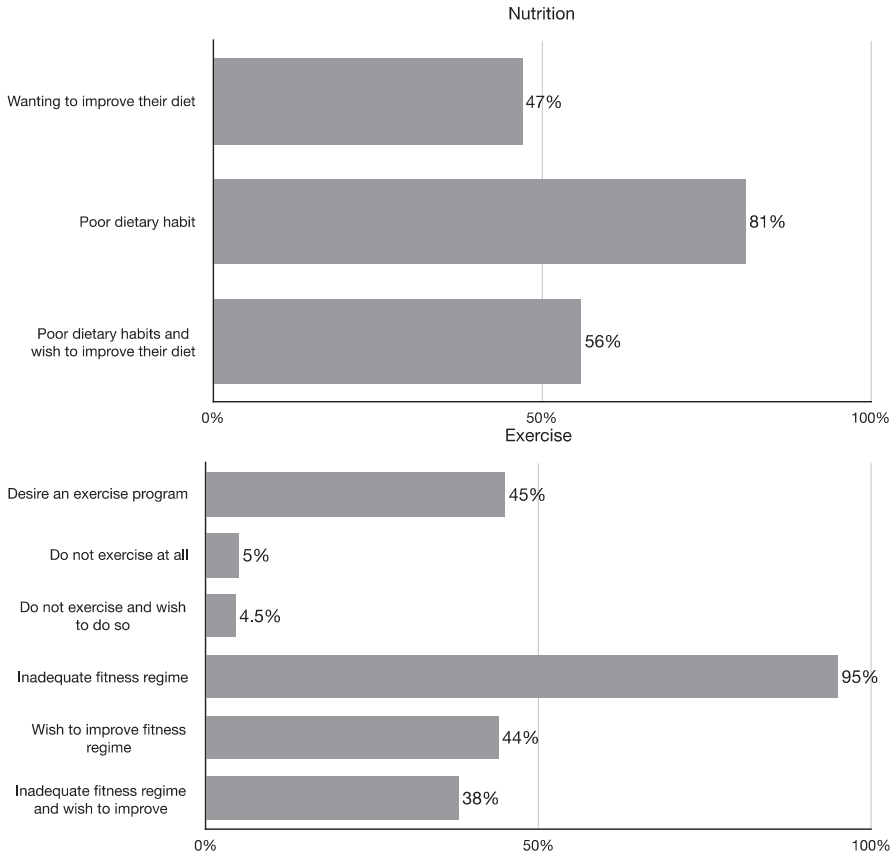
As an employer you can draw certain conclusions from such figures, in deciding what steps to take next in relation to health promotion. Most important among these is the concept of *HIGH RISK/HIGH YIELD.*

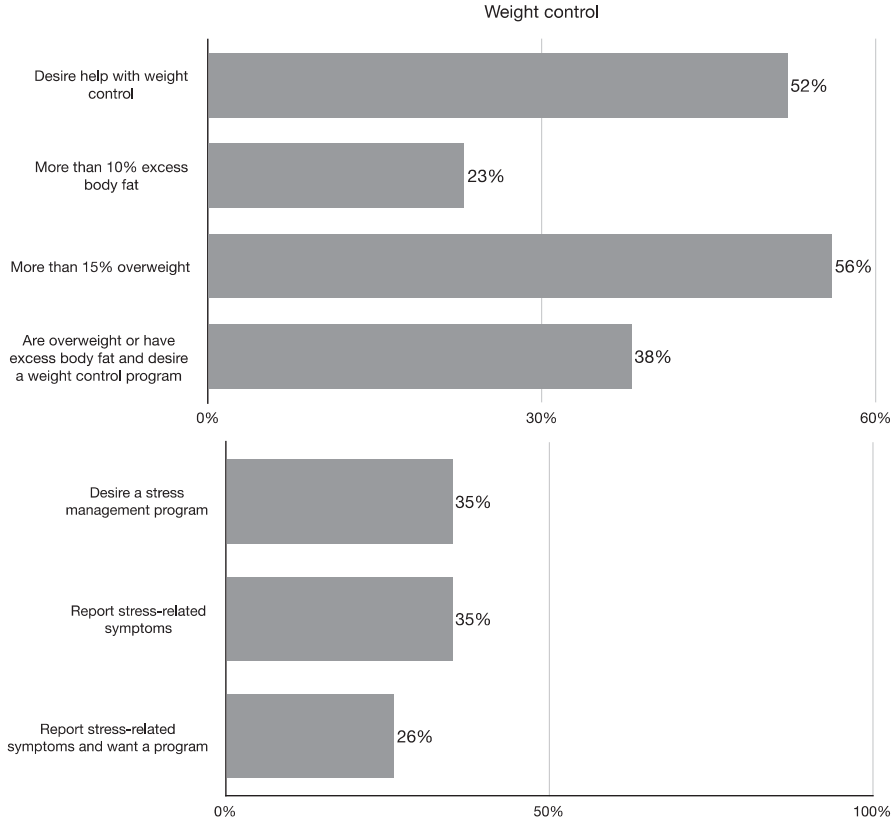
1. Employees with health needs during assistance are the "high risk/high yield" group. They are those at the greatest risk of developing serious (and costly) health problems, but *are also most likely* to make behavior changes *to avoid such problems.*
2. Providing health improvement programs for the "high risk/high yield" group represents the greatest, and most immediate, return on your investment in health promotion-related activities.
3. Making such programs and activities available to all interested employees will also reap valuable returns:
   a. Longer-term payoff for these employees who adopt such activities while they are still healthy and thus avoid many possible future health problems;
   b. Improved morale resulting both from direct benefit of the activities as well as from general employee appreciation for the availability of the activities. (This is usually reflected in reduced turnover and absenteeism, as well.)
4. Participation by other "high risk" employees who were not originally in the "high yield" group will increase as those individuals catch the spirit of the early participant. This phenomenon invariably occurs in companies with successful programs.

Note: This analysis could also be performed in terms of type of employee (executive, managerial and blue/pink collar), or by sex, race, length of employment or other variables.

HEALTH NEEDS AND DESIRE FOR HEALTH BEHAVIOR CHANGES AMONG EMPLOYEES

These tables list the percentages of your company's employees who reported health or lifestyle-related problems and who expressed a desire to make a change related to these health needs.





Appendix D

Unihealth Workshops

UniHealth ... from the University of Maryland, programs to promote a healthier life style

WEIGHT REDUCTION

THE CONCEPT

Scientific evidence indicates that even moderate gains in weight with increasing age are associated with increased health risks without any compensating benefits. This insidious problem of "middle age spread" is difficult to reverse. Therefore, the UniHealth approach to weight control emphasizes prevention.

The program is based on the concept of "energy balance" in addition to the control of caloric consumption. There is strong scientific evidence that gradual weight gain, especially during the fourth and fifth decades of life, results more from decreased activity than from increased caloric intake.

Consequently, the UniHealth approach emphasizes continuation of increased physical activity, combined with moderate caloric restriction, rather than relying upon extreme caloric restriction alone, since this is rarely, if ever, maintained.

UniHealth staff members review individual eating habits and recommend appropriate modifications based on sound nutritional values.

Topics include clinical issues related to food intake and a behavioral approach to facilitate change in eating patterns. The recommended modifications in dietary consumption include reduction in the proportion of total fat (mainly by reduction of saturated fat), and moderation in the use of sugar and salt.

The program is thus suitable for individuals with other medical problems such as high blood fat levels, hypertension, diabetes and heart disease, which are so often associated with obesity. (Weight control programs with special emphasis on either salt restriction or blood cholesterol reduction are also offered).

THE TECHNIQUE

The UniHealth program on weight reduction consists of nine sessions, each two hours in length. The program is divided into three stages: an introductory session, nine health workshop sessions and the maintenance program. An abbreviated version of the program consisting of nine one hour sessions is also offered. Both the one-hour and two-hour sessions are designed for 10 to 12 individuals.

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INTRODUCTORY SESSIONS

In the introductory session UniHealth staff members explain the philosophy and methods of the course in greater detail. Potential participants meet with the staff, have their questions answered and see a cooking class demonstration or sample a recipe. Registration for the workshop program takes place at the end of this session.

HEALTH WORKSHOPS

The health workshops consist of nine weekly one or two hour sessions. Each includes a cooking demonstration using quantities sufficient to provide a light meal to each of the participants.

The desirable body weight, habitual physical activity and caloric requirement are estimated for each individual; blood lipids and lipoproteins are measured at the beginning and end of the course.

Each session is led by a nutritionist and either a physician or behavioral counselor who also address the group at every meeting. The physician discusses the effects of excess body fat on health, and the relationship between diet and blood lipids. He is also available to answer general questions raised by any of the participants. Principles of behavioral modification and their application to the specific objectives of the program are discussed by the behavioral counselor.

MAINTENANCE SESSIONS

One-hour maintenance sessions are offered monthly for all past participants in weight reduction programs. Therefore, a given session may include participants from several different workshops. Participants may continue to attend these seminars as needed.

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INTEGRATED INTERVENTION

THE CONCEPT

Integrated intervention refers to group counseling which is planned to deal simultaneously with blood cholesterol reduction, weight reduction, hypertension control and physical activity.

The strategy of integrated intervention combines factual education and selected elements of behavioral intervention in a group process which is designed to facilitate change in a supportive milieu. While not all of the areas covered may apply to each participant, the group process is enhanced by the sharing of experiences with those who have already overcome some of their problems.

This mode of intervention is particularly suitable for small employee groups which may not provide a sufficient number of individuals to make up complete groups for specific types of intervention.

THE TECHNIQUE

The integrated intervention consists of a two-hour introductory session followed by nine two-hour workshop sessions. Each of these sessions includes a cooking demonstration. An abbreviated version of the series, consisting of ten one- hour sessions, is also offered to meet special scheduling needs; precooked recipes are sampled in place of the cooking demonstrations. The workshops are designed for 10 to 12 individuals.

Introductory Session: The two-hour introductory session is designed to explain in greater detail the philosophy and methods of the program. It also allows participants to meet the staff and have their questions answered. Registration for the educational course takes place at the end of this session.

WORKSHOPS

Health Workshops: The workshop phase of the program consists of nine sessions of two hours each. The weight reduction component includes didactic information and cooking demonstrations. The desirable body weight, habitual activity and caloric requirement are estimated for each individual; blood lipids and lipoproteins are measured at the beginning and end of the course. Each workshop is led by a nutritionist and a physician or behavioral counselor who also addresses the group at every meeting.

The cholesterol component covers the relationship of blood lipids and lipoproteins with atherosclerosis and heart disease, the relationship between diet, blood lipids and lipoproteins, and finally a stepped approach to diet modification designed to lower blood cholesterol.

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The hypertension control component addresses the following topics: causes and complications of hypertension with special emphasis on the role of diet and obesity; and the principles of adherence to regimes of medication and diet.

Maintenance Session: Monthly follow-up sessions are scheduled to reinforce behavior change in all desired risk factor areas.

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PROGRAM EVALUATION

THE CONCEPT

UniHealth offers its subscriber companies an option of program evaluation by the faculty of the University of Maryland Department of Epidemiology & Preventive Medicine.

Program Evaluation provides managers with unbiased and accurate information needed to assess the impact of UniHealth not only on employee health, but also on worker morale and productivity.

Our approach stresses the importance of a scientifically valid evaluation design, identification of appropriate information, and accurate and useful interpretation and generalization of program effectiveness.

THE TECHNIQUE

The UniHealth Program Evaluation is based on discussions with the company, and upon management's goals. Relevant employee health information for program evaluation includes:

1. Frequency of sick leave absences, both planned and unscheduled
2. Total number of days off from work due to sickness or disability
3. Incidence of major disability
4. Utilization of medical care terms of physician office visits, hospital inpatient days, and drug and medication prescriptions
5. Employee-related factors such as job satisfaction and morale

Sources of information for the above include employee records, personal interviews and professional staff assessments.

CONFIDENTIALITY

Assurance of employee confidentiality is vital to the process. UniHealth Program Evaluation Staff uses its authority as an outside consultant to assure that employee responses and medical information are held in the strictest confidence.

A comparative assessment is be made of the cost and benefit of health promotion activities, including the impact of the UniHealth Program on short-term and long-term health, morale and productivity. A health promotion program can be evaluated most appropriately over one and two year study periods.

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REPORTS

University of Maryland UniHealth Evaluations will provide management with quarterly and annual reports which evaluate the effectiveness of encouraging employee participation in the health promotion program and its success in modifying health behavior and improving employee health, morale and productivity.

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CHOLESTEROL CONTROL

THE CONCEPT

It has been demonstrated that epidemics of heart attacks, experienced by millions of Americans in this century, occur in populations which consume large amounts of animal fat. These intakes are associated with high levels of blood cholesterol.

Countries such as Yugoslavia and Japan, which have diets low in animal fat, have been spared epidemics of heart attacks, despite a high prevalence of hypertension and cigarette smoking.

It is also well established that individuals can lower their average level of blood cholesterol by reducing the amount of animal fat and cholesterol in the diet and by eliminating excess body fat.

The UniHealth Cholesterol Control Workshop covers the following areas:

(1) The relationship of blood lipids and lipoproteins to atherosclerosis and heart disease

(2) The relationship between diet, blood lipids and lipo-proteins

(3) A stepped approach to dietary modification in order to lower blood cholesterol level

(4) Discussion and demonstration of recipes from many countries, such as those of the Mediterranean and Asia, where cuisines are highly sophisticated but nevertheless low in saturated fat and cholesterol.
Individuals who are overweight will be urged to attend the weight reduction series, unless enough members of the cholesterol-lowering group are overweight, in which case a combined series may be offered.

THE TECHNIQUE

The basic cholesterol-lowering series consists of one two-hour introductory session and five weekly two-hour workshop sessions followed by monthly maintenance sessions. An abbreviated program may also be offered to meet special scheduling needs; one-hour special introductory and workshop sessions provide samples of precooked recipes in place of the cooking demonstrations. Both the two-hour and one-hour workshops are designed for 10 to 12 individuals.

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Introductory Session: This two-hour session is planned to explain in greater detail the philosophy and methods of the workshop. It also allows the participants to meet the staff and to have their questions about the program answered. Registration for the program takes place at the end of the introductory session.

Health Workshop: The workshop phase of the program consists of five two-hour sessions. Each session includes a cooking demonstration followed by a light meal. The interpretation of food labels and the principles of appropriate food purchasing are emphasized.

Blood cholesterol, triglycerides and cholesterol carried by each of the three major lipoprotein groups--HDL, LDL and VLDL--are measured at the beginning and at the end of the program. The combined cholesterol and weight reduction series consists of nine workshop sessions in addition to the introductory session.

Maintenance Sessions: Monthly follow-up sessions of one hour each are offered for those who wish to participate. The purposes of these sessions are both to reinforce the newly acquired eating patterns and to maintain them through group support.

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HYPERTENSION CONTROL

THE CONCEPT

Among the many prevalent diseases afflicting the heart, kidney and blood vessels, hypertension is by far the most treatable. Although in its earliest stages it may present no symptoms, hypertension (or high blood pressure) can be effectively controlled and its complications prevented.

The UniHealth approach to managing and treating this disease calls for a trial of weight loss for all individuals who are over-weight, a reduction in salt use, moderation in the consumption of alcohol and the provision of adequate dietary potassium and calcium.

The need for drug therapy can often be eliminated, or at least postponed, by applying these measures. Even when drug therapy is necessary, we continue to advocate adherence to the same guidelines in order to minimize the dose of medications, none of which are free of potential side effects.

It is our experience that, with the application of these principles and the systematic selection of the medications most appropriate to each individual at the lowest effective doses, high blood pressure can almost always be safely controlled without serious side effects.

The hypertension workshops provide education on the nature of high blood pressure, its complications, the principles of treatment and the effect of dietary intervention on the control of salt intake and weight reduction.

When medication is considered necessary, the patient will be referred to his own physician or, for those who do not have a physician, treatment by our own specialists can be arranged.

THE TECHNIQUE

The UniHealth group program on hypertension consists of four sessions of two hours each. The program is divided into three elements: an introductory session, the workshop sessions and the maintenance phase. An abbreviated version of the program, consisting of a similar number of one hour sessions, is also offered. Both the two-hour and one-hour sessions are designed for 10 to 12 individuals.

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INTRODUCTORY SESSION

The introductory session is designed to explain the philosophy and methods of the workshop in more detail and to allow potential participants to meet the staff and to have their questions answered. Registration for the program takes place at the end of this session.

WORKSHOPS

The second phase of the program consists of three weekly sessions of one or two hours each.

The following topics will be addressed:

(1) The causes and complications of hypertension with special emphasis on the role of the diet and obesity.

(2) The principles of a low sodium, potassium enhanced eating pattern.

(3) The principles of adherence to regimes of medication and diet.

If a sufficient number of participants are overweight, the course may be combined with the weight reduction course by the addition of six sessions, for a total of 10 sessions. Otherwise, participants who need to lose weight will be advised to attend the weight reduction sessions.

MAINTENANCE

Participants are encouraged to attend monthly follow-up sessions of one hour each. For those receiving drug treatment, a schedule of continuing visits according to individual need is prescribed.

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STRESS MANAGEMENT

THE CONCEPT

Chronic stress imposes heavy costs upon the mental and physical health of employees as well as on an organization's productivity. Coronary heart disease, peptic ulcers, hypertension and alcoholism are a few of the more common stress-related illnesses.

The UniHealth stress management program is a comprehensive effort aimed at altering stressful activities of the employee as well as improving interpersonal relationships and perceptions of the workplace. Because stress is generally an interpersonal problem, it must be addressed in the context of real-life situations.

Accordingly, the UniHealth Program does not place the burden of stress reduction on the individual employee alone, and does not rely on intensive instruction in meditation or relaxation techniques.

THE TECHNIQUE

Stress management can be taught either individually or in the group setting. The program is divided into two phases, an introductory session and the course itself.

Introductory Session: Information is given on the physiological and psychological manifestations of stress, and on the mental and physical consequences of chronic, unrelieved stress.

Workshop Sessions: In the succeeding sessions, the participant's own experience and awareness of stress and ways of handling it are explored through structured exercises. Homework is an essential feature of the program.

Eight sessions of 1 1/2 hours each cover the following:

(1) Understanding psychological and physical stress

(2) The consequences of unrelieved stress

(3) The individual's personal awareness of stress

(4) Ways to change the environment and one's self to alleviate stress--including analysis of coping strategies, vulnerability to particular stressors, life style preferences, time management practices, and career attitudes and planning

Employees may be referred for personal counseling and intensive biofeedback if needed.

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SMOKING CESSATION

THE CONCEPT

Cigarette smoking is now generally recognized as one of the principal health hazards of our society. Unfortunately, there are widely held misconceptions concerning the difficulties of quitting and the effectiveness of intervention techniques.

The department's previous experience with the Multiple Risk Factor Intervention Trial (MRFIT), and other programs, demonstrates that a well-coordinated and persistent approach to smoking intervention is highly effective. The University of Maryland achieved a quit rate of almost 60% after an average follow-up period of 7 years.

The UniHealth approach stresses a high probability of success with proper planning, attitude formation, factual information and mutual support systems. It does not use or recommend aversive techniques or pharmacologic agents.

Hypnosis by a consultant psychiatrist is available to those who do not achieve success with our regular individual or group counseling.

THE TECHNIQUE

The UniHealth Smoking Cessation Program is divided into three stages: preparation for quitting smoking, the quitting process itself and maintenance of quit status.

The group program consists of eight 90-minute sessions. Desirable class size varies between 15 and 25 persons.

Introductory Session: The first session is held one week prior to the Intensive Quit Program. This session has a subtle but powerful impact in motivating participants to tackle the responsibility of quitting smoking.

The Intensive Quit Program: This phase consists of four consecutive day or evening group sessions during the second week of the program. Each session is highly structured, providing comprehensive information on quitting strategies, possible pitfalls and how to avoid them. Also included are the techniques required to maintain a permanent non-smoking status.

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Maintenance Sessions: This final phase of the program consists of three one- hour sessions. The first session is held three weeks after the end of the intensive quit phase, and the other two sessions, three and six months later.

The purposes of these sessions are to reinforce non-smoking behaviors and to review solutions to long range problems such as weight gain and tension.

HEALTH RECOMMENDATIONS FOR YOUR DIET

Beta-carotene

Because your reported diet contains less than the average intake of foods containing beta-carotene, you may be able to reduce your risk of cancer by increasing your consumption of carrots, apricots, peaches, spinach, melon and sweet potatoes.

Other vitamins

Because your reported diet contains less than the average amount of vitamins, you can reduce the likelihood of developing vitamin deficiencies by increasing your consumption of fruit, vegetables and skim milk or cottage cheese so that you have at least one serving of each every day.

Calcium

Because your reported diet contains less than the average amount of calcium, you do not take calcium supplements, and as a white female who does not engage in regular physical activity, you are at higher risk of osteoporosis (brittle bones), you should increase your intake of calcium either by increasing your consumption of skim milk or, if you prefer, taking calcium supplement and establish a habit of regular physical activity (as recommended in the exercise section).

Fiber

Because your reported diet contains less than the average amount of fiber, you can reduce your risk of developing cancer of the colon and certain other diseases by adding bran to your diet either in the form of cereal made with bran or by

adding pure bran to other foods you eat, and by increasing your daily consumption of fruits and vegetables.

The Health-Risk Assessment Questionnaire provides a computer-based evaluation of each participant's current health status. It assembles information on the current lifestyle practices and other health-related characteristics of the individual, estimates relative risks on the basis of published epidemiological studies and mortality tables, produces a printout of the participant's disease risk factors, and summarizes that person's ten-year risk of death from the 12 most common causes of death in populations of similar age, race and sex. Finally, it estimates each participant's overall mortality risk.

After completing the health risk assessment, a *Personal Health Profile and Prescription* is generated by computer for each participant. This document is addressed personally to each individual, and includes specific dietary, behavioral and clinical suggestions recommended by the UniHealth program. An example of the personal health profile and prescription is presented in Appendix B. For corporations signing up with the UniHealth Program, individual personal health profiles and prescriptions are prepared for each participant and a *Corporate Health Risk Profile and Prescription* is prepared for the business as a whole. An example of the format of the *corporate health risk profile and prescription* is presented in Appendix C.

The UniHealth program also offers seven educational sessions, lasting sixty to 90 minutes each, on modifying smoking habits, weight control, blood pressure, salt intake, cholesterol levels, stress, physical fitness and alcohol and drug abuse. The sessions were designed to inform the

participants of modifiable health-related behaviors and to motivate their participation in actual risk reduction programs. Classes are scheduled at the worksite or other locations convenient to the participants. Outlines of specific educational training sessions are presented in Appendix D.

Customized health promotion programs can be created for the unique needs of a business or industry and the program of health risk assessment and health behavior workshops can be supplemented with additional options. For example:

[1] The basic health risk assessment questionnaire can be supplemented with additional modules addressing cardiovascular fitness, physical fitness or screening for defined preventive medicine purposes.
[2] Selected physical measurements and laboratory findings can be added.
[3] Sub-groups of participants at high risk for cardiovascular disease, diabetes or other diseases can be identified and offered further evaluation.
[4] Exercise prescriptions can be prepared and high-risk patients referred for stress testing.
[5] Educational programs relating to fitness and health promotion can be offered to employees and their spouses.
[6] Other program evaluations and management reports can be prepared, as needed.

The UniHealth Program was designed as a departmental program, but faculty from other medical school departments will also be involved: blood and urine specimens to be tested by a laboratory department; X-rays will be taken if recommended; participants needing clinical care will be referred as needed; and hospitalizations will take place as necessary.

CHAPTER SIXTEEN SUMMARY

THE NATIONAL CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE

After developing the health promotion program, the health risk assessment questionnaire, and UniHealth, the department embarked on efforts to create a university-wide central facility for all these activities, including extensions to UMAB schools and the central campus at College Park. The newly arrived UMAB Chancellor, Dr. T. Albert Farmer, Jr., strongly supported this decision and was key to the involvement of University President Dr. John Toll and Robert G. Smith, President of the University of Maryland Foundation.

In contrast with the other initiatives described in this volume, establishing the National Center was a completely political process, far removed from any prior or future activity in my professional life. It was a major venture into the world of politics, even though it was situated within a major medical center and university. I was not fully prepared for this enterprise, although it required endless hours each day for many months to pursue the tasks assigned by the political figures in this melodrama.

After the substantive program of the proposed National Center was formulated, communicating its purposes and soliciting the active participation of faculty, staff, and students in all UMAB departments became a formidable task. So too was the need to stimulate the long-term commitment of the

university leadership, attract funds, provide a centrally located headquarters building, develop an effective public relations campaign, solicit prominent supporters, and plan for a widely publicized series of public announcements, inaugural dinners, and other highly visible events promoting the Center's establishment.

The highly dramatic finale to this narrative, while totally unexpected, may explain the reluctance of many in academia to venture into the political realm of biomedicine.

CHAPTER SIXTEEN

THE NATIONAL CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE

BACKGROUND

After developing our health promotion, health risk assessment, and UniHealth programs, the department was encouraged by the university to unify all of these activities into one National Center at a location midway between the campuses in Baltimore and the Washington DC suburbs. The newly appointed UMAB chancellor, Dr. T. Albert Farmer, Jr., strongly supported this enterprise and was key to the involvement of University President John Toll and Robert G. Smith, President of the University of Maryland Foundation.

The rationale for establishing a National Center for Health Promotion and Preventive Medicine was described at a conference entitled: "A Sea Change in Attitudes Toward Public Health." Agreement was reached that the major issues to be addressed by the National Center would include the following:

1. **Greatly expanding our existing programs in health promotion, health risk assessment and UniHealth**.
2. **Improving the quality of reporting on health and environmental issues** by the press and other public media.

3. **Modifying the impact of health and environmental regulations enacted by federal agencies (like OSHA, NIOSH and EPA) and state governments**, whenever the intended outcomes fail by serving political ends rather than addressing substantive health problems.
4. **Confronting the significant increase in litigiousness in broad arenas of public health.** Thousands of lawyers are now employed full-time in filing lawsuits for clients claiming to have a disease, a pain, or other negative outcome after exposure to substances that theoretically might be a risk factor for disease. Examples of the latter include: Agent Orange in the military; brain cancer in Olin chemical workers; breast cancer in hair-dye exposure; the Dalkon Shield in Ob/Gyn disorders; Rely tampons in toxic shock syndrome; and Maryland workers minimally exposed to asbestos.

A number of other beneficial services for specific sectors of the commercial world could also be offered:

1. **For commercial companies and industries:** The Center could develop automated clinical information systems to track the health behaviors and disease histories of employees in specific companies, from the time of their hiring to retirement and beyond. It could publish monthly bulletins on newsworthy health or disease topics of interest to the industry. Video films, slide shows, and manuals on specific health topics could be produced by the Center. It could design prevention and intervention measures for worksite health problems as they arise. Some employees could be attracted into our health risk assessment and health promotion programs, or be referred to appropriate University of

Maryland clinical departments for diagnosis and treatment of a medical problem. The scientific core faculty of our Department of Public Health would always be prepared to institute etiological investigations of any disease of interest to a participating industry, including clinical trials of new drugs, devices, and medical technologies.

2. **For hospitals and clinics:** Under the aegis of the Center, automated clinical information systems like those prepared for the Academy of Dermatology could be developed for hospitals and medical clinics. The personnel required for such projects—epidemiologists, clinicians, statisticians, computerniks, and an array of coders, interviewers, and assistants for such projects—are already members of the department and their number could be easily supplemented, given the department's reputation and its central location between Baltimore and Washington DC.
3. **For health insurance companies and third-party payers:** Such firms are constantly seeking ways to promote health and reduce the costs of medical care. These are precisely the same goals of the National Center, which could achieve them at substantially lower cost than commercial companies. Selected firms might also be interested in having the Center study health perceptions, behaviors, suspected health hazards, trends in disease incidence, correlations of disease with toxic or other environmental factors, etc. as part of their effort to control healthcare costs.
4. **For schools and colleges:** The Center's health education and health promotion activities could be readily applied to satisfy the needs of schools, colleges, labor unions, and voluntary organizations. A national speakers bureau could be assembled to lecture on

occupational health and preventive medicine. Our proximity to the nation's capital greatly simplifies identifying and recruiting such lecturers beyond the department's own faculty.

5. **For federal and state governments:** Many legally mandated government obligations in health promotion, health risk assessment, and occupational and environmental medicine are being discussed and researched in the department. Additional health mandates from federal or state agencies could easily be added to the department's existing program.

After the initial meetings and conferences led the university to approve the establishment of the National Center, arrangements had to be clarified with each department in the medical, dental, pharmacy, nursing, and law schools on campus, and detailed discussions had to be initiated with the faculties and administrative leadership at the main university campus in College Park. Perhaps a year was spent introducing the concept of a university-wide National Center, sounding out the individual school faculties and coming to understandings with deans, chairmen, hospital program directors, and university administration officials.

A higher echelon level of meetings, discussions, and agreements were those involving the university president, the UMAB chancellor, the president of the University of Maryland Foundation, and their associates. It was at these conferences that initial and long-term funding issues, present and future locations of the Center, and identification of prominent figures that might be willing to associate themselves with the Center and its purposes were discussed. (Figure 1). Among the decisions made was an inauguration of the National Center at a major reception to be hosted by the

nationally prominent Clare Booth Luce, locating the clinical and research offices at the medical school, and construction of central administrative offices in a new building on Route I-95 in Laurel, Maryland, strategically located within a 30-minute drive of Baltimore, Washington DC, and their two principal airports (Figures 2 and 3).

The frenetic pace of these activities reached a fever-pitch at the university during 1984 when University Hospital neared approval for its re-designation as a private hospital—a somewhat political decision since its original establishment as a state agency in 1807—and the inauguration of the National Center was on the verge of being formally announced. At the time, I was serving as a member of the Council of Clinical Chiefs at University Hospital, a trustee of the Board of Trustees of the Medical Faculty Foundation, and a member of the Advisory Committee of the University Cancer Center, all of which were involved in the proposed hospital re-designation as well as the National Center.

My involvement in the intense political activities described above did not interfere with continuing as chairman of a large academic department, but began to suggest that I might be nearing the limit set by the well-known "Peter principle." For several decades I had pursued a career that was all-consuming as well as personally satisfying. The first half of this period was devoted to classical epidemiological research, identifying public health issues of concern, reading the current literature, developing etiological hypotheses, applying for funds, conducting research, analyzing findings, and reporting the results to medical colleagues, fellow epidemiologists, students, and the public at large. The second half drew me into higher levels of academic administration, and exciting opportunities arose to apply newly developing computer

technology to the largely unmet needs of public health and preventive medicine.

Chancellor Farmer arrived on campus several years after our vision of a new era in epidemiology linked to the flowering of computer technology was being implemented. The comparative study of dermatological care by two medical specialty groups had been completed, and the faculty was turning its attention to developing clinical information systems. Health risk assessment programs were being offered to physicians as well as Baltimore-area commercial firms. Dr. Farmer heard about this, and was wholeheartedly approving of the new directions the department was pursuing. This was a remarkable development for a medical school department that is universally considered a minor actor in all, or most, medical schools. Securing active cooperation between such a department and a university chancellor is, and has always been, a rare event; even more so when the department generates little clinical income, and is not considered central to the primary mission of most medical schools.

I accepted Dr. Farmer's assistance with much gratitude, as I did the subsequent involvement of University President John S. Toll and the University of Maryland Research Foundation President Robert G. Smith. These officials agreed that the National Center could become a major asset to the university and the nation. Subsequent to receiving their enthusiastic approval, the department began to engage chairmen and faculty individually about the expected benefits they could expect from the clinical and diagnostic services to be offered to companies enrolling in various Center programs. We then began turning our attention to securing active participation of the dental, nursing, and pharmacy schools, and spreading the information to the other campuses of the university. The

UniHealth program had already developed a number of new health risk assessment instruments, which were being utilized on a trial basis by some Maryland companies, community health fairs, private practitioners, and small groups of senior medical students. Our faculty members also assumed responsibility for producing test versions of health promotion newsletters for the Maryland Department of Health and Mental Hygiene and the Maryland Department of Personnel.

Several million dollars' worth of funded research projects in health promotion and disease prevention were underway, dealing with hypertension control, alcohol in pregnancy, drug abuse, smoking cessation, nutrition, osteoporosis, the elderly, and congenital heart disease. The Maryland Cancer Registry and the Maryland Gerontological Association were fully established and their programs were well underway. The department's undergraduate and graduate teaching programs for medical residents, medical students, nurses, pharmacists, social workers, and others preparing for careers in health promotion and disease prevention were already supplying future manpower for this growing field.

A site had been tentatively chosen for the Center's central administrative headquarters midway between Baltimore and Washington DC, and the university was planning to announce the Center's establishment at an inaugural reception, possibly at the home of the national figure Clare Booth Luce. In the midst of this exciting transition, I was completely unprepared for what was perhaps the most shocking and devastating event in my career: the sudden and completely unexpected death of UMAB Chancellor T. Albert Farmer on April 10, 1984. Communication with Dr. Toll and Mr. Smith ended almost instantaneously, and Dr. Farmer's replacement arrived a few months later, with minimal understanding of, or enthusiasm

for, the National Center.

Though regular meetings of the upper-tier university administrators were no longer held, we continued faculty-level discussions for another year and prepared a grant proposal to the Centers for Disease Control for supporting the basic elements of the Center. The proposal was not strongly supported by the new UMAB administration, although the new chancellor's name appeared on the cover of the latest version of the National Center brochure. With university support disappearing and federal funds not forthcoming, our efforts to create a university-wide collaborative institution for health promotion and preventive medicine ended. To our knowledge, no comparable effort exists elsewhere to continue such efforts. (See Chapter 19 for our final recommendations concerning the National Center.)

Looking back at the intense efforts made, the excitement generated, and the enormous support garnered, I have no doubt that another medical or public health school with staff and resources comparable to ours could succeed in creating a similar National Center.

Figure 1: Initial form of the National Center brochure

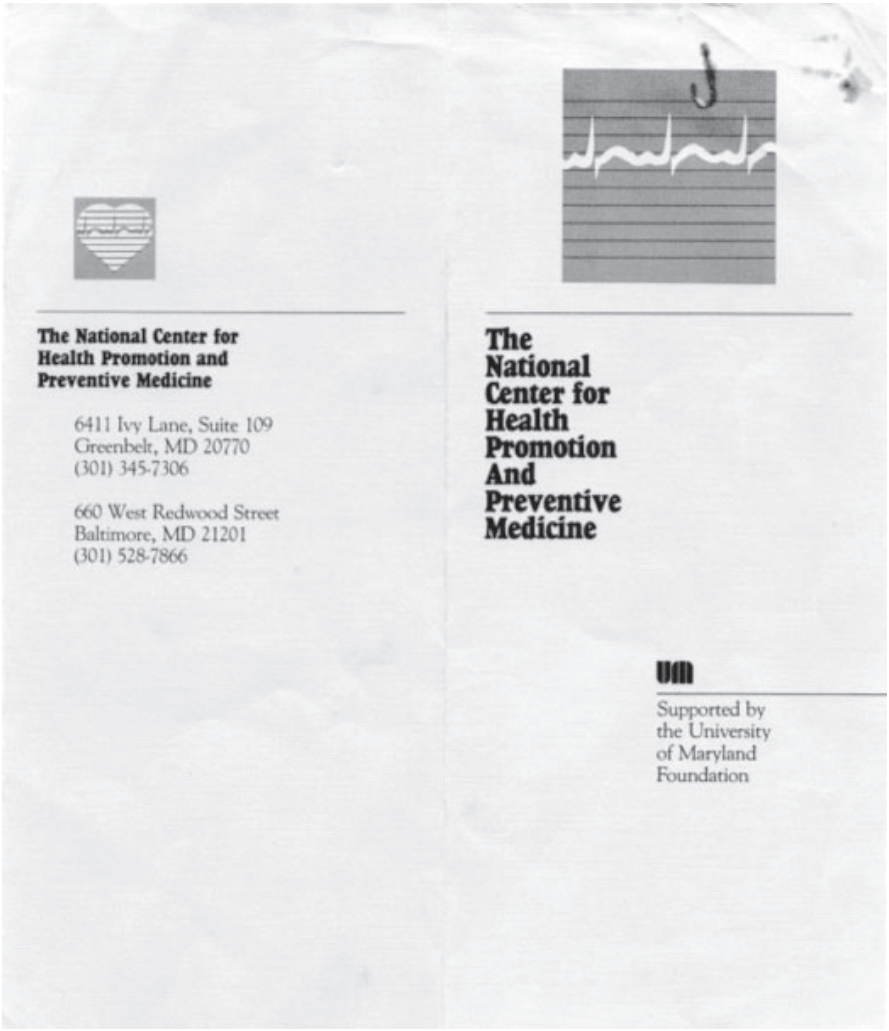


Figure 2: Konterra: The Designated Location of the National Center

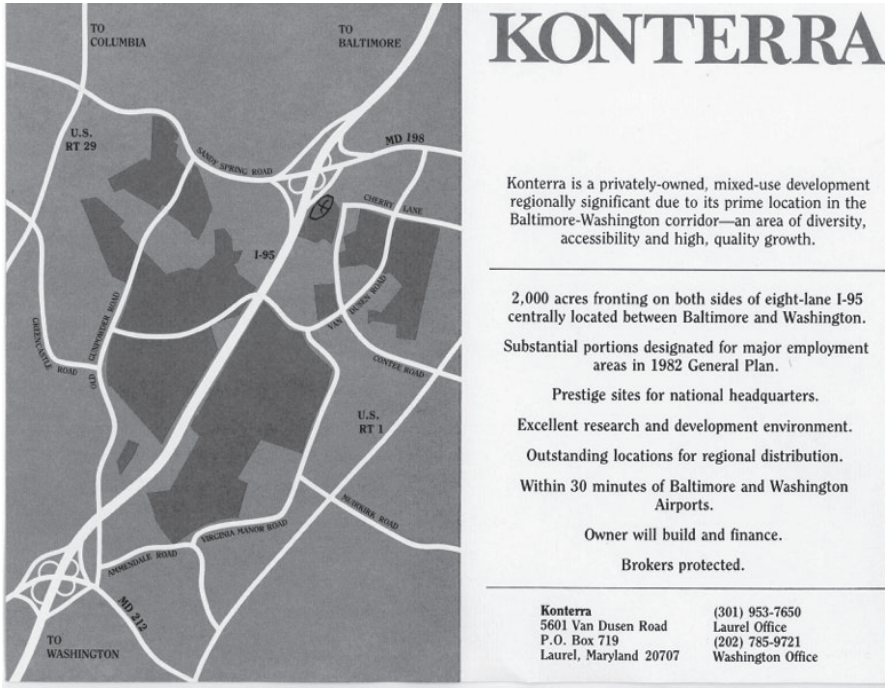
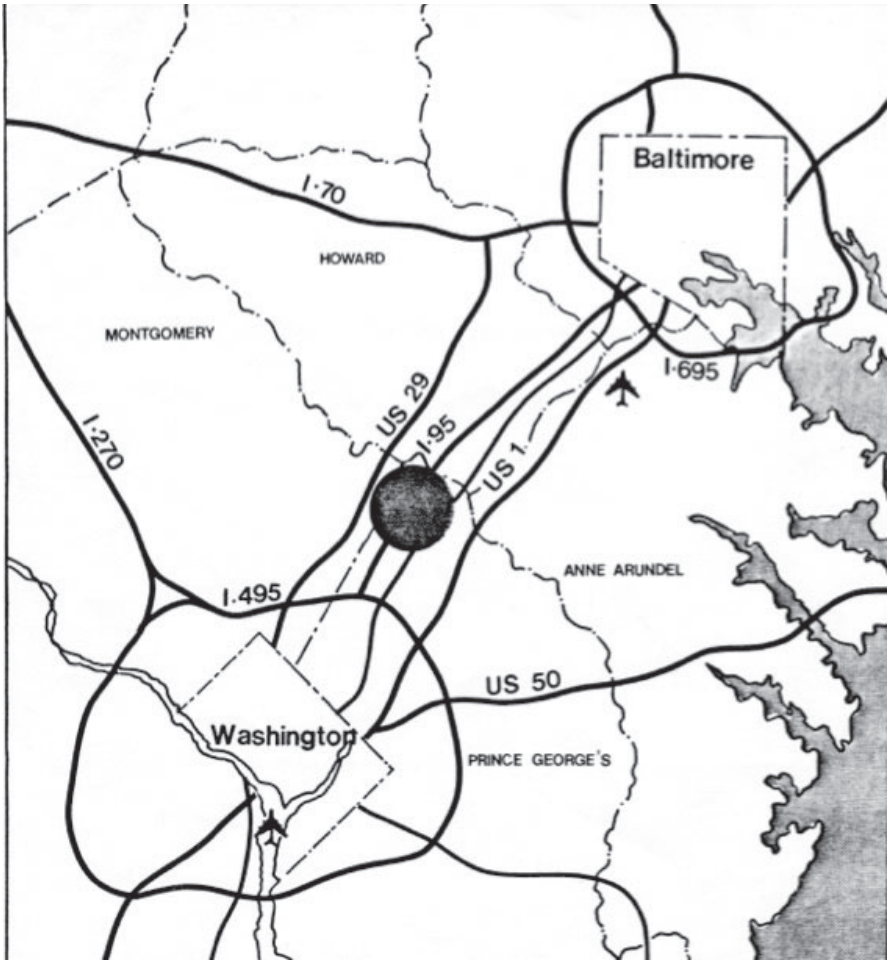


Figure 3: Location of National Center Midway between Baltimore and Washington D.C.



CHAPTER SEVENTEEN SUMMARY

DEVELOPMENT OF A HEALTH TECHNOLOGY ASSESSMENT SERVICE

New drugs and health technologies are being developed and offered to the public at a more rapid pace than ever before. While the federal government has allocated funds for agencies like the FDA to certify the safety and utility of such products, there is no doubt that the process is far from perfect and that misjudgments are being made. Details on a few examples of the latter may be found earlier in this volume (Chapters 2 and 8).

A short-term arrangement with a Philadelphia non-profit firm allowed me the time to consider creating a health technology assessment service for them. We applied for a federal grant that was initially unfunded, but nevertheless we began developing an academic unit in our department to address this important national problem.

The core function of a health technology assessment (HTA) service is to produce objective evaluations of new health technologies for use by the healthcare industry, government, and academia. Our service was planned to have four cores: **an administrative core** to conduct the business; **a bibliographic core** to search all possible databases; **an analytic core** to evaluate incoming data and produce assessment reports; and **an informatics core** to operate a computer-based system to collect, configure, and communicate with other databases

holding data of potential value to the assessment service.

The HTA service would involve faculty from most medical school departments working rather closely together. The Oversight Committee was to have the following members: medical school dean, university hospital director, university medical library director, National Library of Medicine representative, Agency for Healthcare Research and Quality representative, two senior clinicians from other departments of the medical school, and four senior members of the Department of Preventive Medicine.

CHAPTER SEVENTEEN

DEVELOPMENT OF A HEALTH TECHNOLOGY ASSESSMENT SERVICE

BACKGROUND

The rate at which new drugs and other health technologies are being developed, patented, and offered to the public has never been greater. While federal agencies such as the FDA have established a regulatory system for certifying and marketing these products, there is no doubt that their decisions are sometimes illogical, politically influenced, or otherwise inappropriate. At the same time, there are very few non-profit institutions that are capable of undertaking objective assessments of these technologies. Our department, a haven of clinically sophisticated epidemiologists, biostatisticians, and computer technologists, with direct access to other clinicians, a range of bioscientists, and a large medical library, is an outstanding exception to the rule.

I had been associated with a Philadelphia firm that expressed an interest in offering health technology services to supplement their existing business. This experience motivated us to apply for a federal grant to develop a broadly based non-profit health technology assessment (HTA) service, after discussions with epidemiology colleagues and clinicians in the Medical School. After the proposal went unfunded, we modified the plan to create a new departmental HTA service of clinically trained epidemiologists and highly motivated

clinical and basic science faculty to promote this long-neglected field.

The core function of the new HTA service would be to analyze and rapidly produce comprehensive and valid evaluations of new health technologies for the use of the healthcare industry, academia, and government. The service would have four cores:

A. The Administrative Core, to provide administrative support for the fiscal, staffing, public relations, marketing, publishing, and educational programs of the HTA service. Its functions would include:

1. **Conducting the business aspects**;
2. **Managing the human resource aspects**;
3. **Administering the academic aspects**, including assignment of staff, students, fellows, and faculty to HTA projects; recruitment of extramural senior HTA consultants; organizing HTA meetings, seminars, and short courses; representing the HTA service to the International Society of Technology Assessment in Health Care, and other professional and governmental bodies dealing with technology assessment; and helping to plan new HTA-related services for educational, professional, industrial, and governmental use;
4. **Negotiating with publishers**, overseeing manuscripts for publication in peer-reviewed journals and a proposed HTA journal; and preparing materials for the press and other print and visual media;
5. **Developing public relations activities to promote the HTA service** to the health insurance companies, HMO's, medical centers, governmental agencies, academic institutions, and the general public; and

6. **Marketing and negotiating HTA services** and products with for-profit and non-profit organizations, and with governmental entities.

B. The Bibliographic Core, to search databases and other bibliographic materials for literature references, citations in the gray literature and other information needed to produce the HTA Reports. Its functions would include:

1. **Negotiating with database proprietors for access** to the potential databases;
2. **Identifying all requisite databases**, governmental and proprietary, for each assigned health technology evaluation;
3. **Assuring access to the database** and configuring telecommunications between the Bibliographic Core and the Analytic Core to meet the needs of the HTA service;
4. **Developing rapid and cost-effective methods to search databases** and identify requisite citations (by type, title, summary, or whole-text, as required) for each health technology being reviewed;
5. **Developing cost-effective methods to recover citations** in formats optimally amenable to their analysis by the Analytic Core staff;
6. **Creating a database of technology discoverers**, patent holders, research scientists, manufacturers, regulatory agencies, media, and other entities for each assigned health technology, coded by type of entity, for use by the Analytic Core;
7. **Developing proposals to enhance research at the medical school's health sciences library** and extramural institutions, by adapting selected features or products of the HTA service;

8. **Adapting the HTA service to enrich the training of health science library students** (e.g. on-site and off-site training through a network and educational materials, both hard copy and PC/CD-ROM-based).

C. The Analytic Core, to analyze the information supplied by the Bibliographic Core, and produce valid assessments of new health technologies for the use of the healthcare industry, academia, and government. Its functions will include:

1. **Senior HTA consultants designing the formats of the HTA Reports**; assigning HTA analysts to specific tasks described below; and supervising the completion of the projects;
2. **First-level HTA analysts reviewing the citations identified by the Bibliographic Core** for each technology and assembling preliminary write-ups for each section of the planned HTA Report;
3. **The preliminary write-up described above would follow a semi-automated format devised by the senior HTA consultant together with colleagues in the Bibliographic and Informatics Cores**. The format will automatically classify each citation, reviewer comment, and text quotation in the appropriate section of the planned HTA Report; permit quick merging and transfer of text and files; facilitate the construction of spreadsheets, graphs, and figures by the analysts; and codify and print references in the requisite format. The system will also differentiate the text into sections deriving from published sources, the grey literature, and the views or opinions of individuals, including the HTA analysts or consultants;
4. **A first- or second-level analyst will be assigned to communicate with discoverers, patent holders,**

manufacturers, regulators, research scientists, medical writers, and others whose views or tendered information have been cited for the assigned health technology and recovered by the Bibliographic Core. Data, statistics, opinions, and all other relevant information concerning the new technology produced, published, or aired by these individuals will be incorporated into a preliminary draft of the HTA Report, using automated procedures similar to those described above;

5. **Preliminary drafts of the HTA Report will be assigned to faculty consultants, intramural or extramural, and then to second-level analysts** for preparation of penultimate HTA Reports;
6. **Preparation of the final version of the HTA Report will be the responsibility of the senior-level consultant**;
7. **Products of the HTA service will be adapted to enrich the education and field training of MS and PhD students in epidemiology, biostatistics, and medical informatics, as well as graduate students, fellows, and postdoctoral trainees** from other UMAB schools and departments and beyond. Included will be programs for on-site and off-site training through the network, and the preparation of educational materials in hard copy and PC/CD-ROM-based versions.

D. The Informatics Core, to plan, develop, and operate the network system, software, and hardware, as required by the HTA service. Its functions include:

1. **Cooperating with the Bibliographic Core director in negotiating with database proprietors for access to their databases**;

2. **Assuring that database access between the Bibliographic and Analytic Cores are configured to meet the needs of the HTA service**;
3. **Collaborating with the Analytic Core in developing an automated format for the initial review and write-up of the HTA Reports**, as outlined above;
4. **Collaborating with the Analytic Core in developing an automated system for recording and analyzing information obtained from the discoverers, patent holders, manufacturers, regulators, research scientists, media, and others cited for the assigned health technology and its incorporation into first-level write-ups of the HTA Reports**;
5. **Developing an automated system to manage the administrative aspects of the HTA service**, including budgets and personnel. The system will also keep track of days devoted to each HTA Report by category and level of staff member or consultant, in order to generate reliable estimates of production costs; and
6. **Adapting appropriate elements of the HTA service to enrich the training of graduate and professional students in medical informatics**. Included will be programs for on-site and off-site training through the network, and the preparation of educational materials in hard copy and PC/CD-ROM-based versions.

An Oversight Committee will provide oversight and strategic planning for the HTA service, with the following membership:

Office of the President, UMAB;
Office of the Dean, Medical School;
Representative, National Library of Medicine;
Representative, Agency for Healthcare Research and Quality;

Representative, University of Maryland Medical System Foundation;
Chairman, Department of Preventive Medicine;
Director, Bibliographic Core;
Director, Analytic Core;
Director, Informatics Core;
Director, Administrative Core Ad Hoc members: Two medical school tenured clinicians.

CHAPTER EIGHTEEN SUMMARY

MARKETING STRATEGIES FOR A UNIVERSITY HOSPITAL

As the department evolved into a multidisciplinary public health educational and research facility, our faculty often asked why we were rarely invited by University Hospital to undertake data analyses or to help develop strategies for marketing its healthcare services to the general public. At the time, a host of for-profit companies had already assembled staffs to offer their marketing services to hospitals, which they were advertising widely.

Advances in computer technology were the basis for these commercial solicitations, even though the firms usually lacked the medical and hospital expertise of academic departments like ours. We suggest that our involvement in marketing would have three distinct advantages over a commercial alternative: (1) the cost would be lower than any commercial alternative; (2) our department is substantially knowledgeable about hospital data systems which they repeatedly access, while the commercial alternatives have little or no exposure to them; and (3) our department will obviously remain on campus and be available to deal with subsequent problems, and the inevitable need for modification and adaptation, whereas the commercial firms will have long departed from the campus.

On one occasion Maryland's University Hospital invited our department to undertake a study and prepare a marketing strategy for their review, though without any funding for the project. The faculty engaged in this analysis for several weeks and produced a detailed report suggesting actions the hospital should undertake in the near future. The hospital then surprised us by hiring a commercial company at the usual inflated price, and the firm then requested that we send them copies of our completed hospital analysis. The commercial company's final document to the hospital closely resembled our report, although it had been finely illuminated and printed on much higher-grade paper than used by our department. The details of this report, demonstrating the capabilities of departments like ours in producing such reports, are provided in this chapter.

CHAPTER EIGHTEEN

MARKETING STRATEGIES FOR A UNIVERSITY HOSPITAL

BACKGROUND

As the Health Data Management Center (HDMC) began to grow in size and quality, we began to meet with University of Maryland Hospital officials to discuss their needs for data and analysis, as the hospital was moving toward independence from state government control. There was an obvious need for the hospital to strengthen its marketing of clinical services more effectively to the Baltimore City community and beyond. It also needed to upgrade its inadequately functioning clinical information system. Yet, for all of its renowned clinicians, the medical center had very little experience or capacity in developing such systems on its own.

The Department of Preventive Medicine should have been the logical choice for the hospital to turn to at this juncture: we had become one of the nation's premier public health centers, with a large faculty of epidemiologists, biostatisticians, social scientists, computerniks, and clinicians who were teaching growing numbers of graduate students, and were engaged in basic and applied research in many aspects of healthcare. Yet, despite numerous efforts on our part, we were almost never solicited for assistance by the hospital. The dominant, and favored, competition was from commercial firms.

At the time, a host of for-profit companies had begun making elaborate visits to hospitals, clinics, and even individual practitioners, with proposals for computerizing their clinical information and billing systems as well as marketing their healthcare services. Advances in computer technology had begun to make such solicitations profitable, and it was not difficult to establish companies that posed as experts in clinical information systems, even though they lacked the medical and hospital expertise of a department like ours.

On the one occasion that the hospital seemed willing to deal with us, we were in fact competing with a commercial company that lacked any depth in healthcare-related achievements, but arrived on campus with a large staff, beautiful colored brochures of their advertised products, and well-rehearsed salesmen. They eventually submitted a reputedly million-dollar proposal to the hospital.

Our department's counter-proposal was based on a number of verifiable facts:

1. **The cost of our proposal would be lower by hundreds of thousands of dollars**,than the commercial alternative.
2. **Our faculty and staff were completely knowledgeable about, and had been utilizing, the hospital's existing data system for many years.** The commercial alternative spent a few days listening to hospital staff members describe their system, but remained largely strangers to it.
3. **Our department is a permanent component of the medical campus.** Creating a new clinical information system for a major medical center is fraught with problems that often appear long after the project has

been completed. In such circumstances, having the developers permanently on campus to make adjustments and revisions is a major advantage for the hospital.

4. **After any new system is installed, there will arise over time a host of changes and improvements that will be demanded.** Once again, having the developers of the system on campus is a major advantage.

The department's failure to win a contract from the hospital was due to several reasons:

1. **Our multidisciplinary nature and pioneering efforts in healthcare research and training were probably never fully understood by the hospital**, which dealt primarily with the clinical departments.
2. **A critical deficiency of funds to promote and advertise our services**, capabilities, and experience to the outside world, including the university hospital.
3. **The hospital was probably not fully aware that we were ready to compete with commercial companies to satisfy a variety of the medical center's analytical needs.**

We present below major elements of the report that our department prepared for the hospital and offered to them without cost.

EXECUTIVE SUMMARY

The University of Maryland Hospital (UMH) is an 864-bed (60-bassinet) teaching hospital, located in Center City, Baltimore, Maryland. It was established in 1832 to provide medical care to residents of Baltimore and to serve as the principal teaching hospital of the State's medical school,

founded in 1807 as the country's first public medical school. At the time of this report, UMH was running major deficits of $7 million in fiscal 1981 and over $8 million in fiscal 1982.

The Vice Chancellor of the University of Maryland Medical System was considering a variety of strategies to return the Hospital to fiscal solvency. Its review of UMH operations, and the market in which it operates, is based on our department's Health Data Management Center report, "Present and Projected Patterns of Hospitalization at University of Maryland Hospital" (1986). The major elements of the operating environment, classified by opportunities, strengths, threats and weaknesses, are summarized in Table 1.

Table 1: The Current UMH Operating Environment

I. Opportunities	*III. Weaknesses*
a. Economic re-development of Baltimore is underway	a. Reliance on Medicare, Medicaid and Charity
b. Growth in Outer West, and Outer South suburbs	b. Suboptimal average daily census
c. Cardiology care	c. Inadequate public relations
II: Strengths	*IV: Threats*
a. Tertiary care	a. Reduced government outlays for Medicare, and Medicaid
b. Emergency services	b. Declining 0-18 year old population
	c. Non-referrals from affluent suburbs
	d. Declining patients/patient days
	e. Declining population of Baltimore
	f. GIR pricing regulations

Five policy issues presently challenge the fiscal management of UMH:

A. *Patient Mix Balance:* The UMH patient load has traditionally been weighted toward indigent patients and those reimbursed through Medicare and Medicaid. Conversely, the Hospital has not attracted a sufficient representation of privately insured patients. This imbalance is aggravated by an increasing probability that federal support for Medicare and Medicaid programs will be reduced in 1983 and 1984.

B. Low Daily Census: In recent years, UMH has generated fewer than 168,000 patient days per year, considerably below its capacity. Higher utilization rates would reflect more efficient use of fixed assets and could substantially help reverse the negative cash flow problems.

C. Declining Urban Demand: Baltimore City, the venue of UMH, accounted for 58 percent of patient admissions in 1979 and is the primary market of UMH. The city's population is expected to decrease by approximately 11 percent between 1979 and 1986, i.e. by an annual average of 1.57 percent. Consequently, the UMH patient load, expressed as patients and patient days, may be expected to decline an additional 3 percent and 2 percent, respectively, between 1979 and 1986.

D. Rapid Growth in Suburban Markets: While demand for UMH services by Baltimore City residents is falling, the needs of the suburban communities are expected to grow vigorously during the 1979-1986 time period. This should be considered a crucial challenge to UMH management, because explicit strategies to increase services to the suburban growth segments have yet to be developed. In particular, data from our Health Data Management Center suggest that UMH should target the

Outer West and Outer South geographical areas for enhanced marketing efforts.

E. *Public Relations:* In its present status as the "other" University Hospital in Maryland, UMH may be described as conducting its business "in the shadow" of a colossal neighbor to the East, while striving for greater recognition and utilization by residents of the Greater Baltimore area. For pressing fiscal, and perhaps other, reasons, UMH is supported by a rather limited public relations program at present. In contrast, the Johns Hopkins Hospital is served by a public relations staff of some 15 full-time professionals. It is clear that UMH must strengthen its public relations efforts if it intends to attract a greater proportion of the privately insured patients in this geographical region. *Action strategies should be developed to deal with each of the* foregoing problems. Three, in particular, are recommended by the Health Data Management Center, viz.

[1] Modifying the prevailing patient referral patterns, by actively encouraging physicians to refer their privately insured patients to UMH;

*[2] Augmenting medical services and facilities that are likely to attract privately insured patien*ts, and modifying existing programs with the same objective in mind;

[3] Enhancing the positive image of UMH in the markets that it wishes to serve. Our final report to UMH presents detailed tables on the distribution of patients by clinical specialty among all Maryland hospitals; the geographic origin of UMH patients within Maryland; their payer mix; the market share of each hospital within a 5-mile radius of UMH; forecasted growth or decline in demand for UMH service, by specialty; forecasted growth or decline in

hospital admissions by geographic origin of patients; and projected growth or decline in demand for services by patient payer category. The report concludes with a discussion of opportunities, threats, strengths and weaknesses for UMH:

> *Opportunities:* Perhaps the greatest opportunity for UMH development derives from its location in Center City, the focus of economic redevelopment in Baltimore. Improved parking facilities, a new subway system and completion of Interstate Route I-95 will all serve to make UMH an increasingly attractive site for diagnostic services and high-level hospital care. The institution's proximity to new businesses, middle-class housing and hotels should also increase its potential for enlarging the base of paying patients. UMH can take additional steps to improve the payer mix by increasing referrals of patients from the South and West suburbs. The West appears especially attractive because it is presently the site of only one hospital, Kernan, presently devoted solely to orthopedic services. In respect to other specialty areas, opportunities to improve payer mix abound, e.g. by further developing cardiology services for patients who are especially likely to be privately insured.
>
> *Threats:* Changes in federal government policies—not yet fully effectuated—represent perhaps the greatest short- and mid-term threats to UMH. Cutbacks in funding for the Medicare and Medicaid programs, upon which a preponderance of UMH patients presently depend, have the potential to drastically reduce hospital revenues.

> Government recisions in urban development action grants (UDAGs) could delay or cripple redevelopment plans for the City and, in the process, adversely impact upon future prospects for UMH. In general, the present state of the economy poses a serious threat to the future of UMH. As unemployment increases, fewer patients can be expected to afford commercial health insurance. In the short run, the noise and inconvenience associated with major construction in the immediate vicinity of the hospital could also discourage patients from seeking care at UMH.

Our demographic projections of declining numbers of patients in the pediatric age groups could also portend shrinking revenues because of the emphasis on newborn care at UMH. The paucity of patient referrals by physicians from the East and more affluent North suburbs is another problem. The Maryland Rate Setting Commission's adoption of the Guaranteed Inpatient Reimbursement System based on Diagnostic Related Groups (DRGs) could, by reason of its restrictions on allowable fees, reduce future revenues. The use of DRGs results in pigeonholing each patient into a single diagnosis, regardless of the actual number of clinical conditions treated. Thus, if complications require additional services, less than complete costs are likely to be recovered.

> *Strengths:* A widely recognized asset of UMH is its highly developed Shock Trauma Center. Beyond this and the Cancer Center, the establishment of additional clinical centers of excellence should be under active consideration in specialties including perinatology, cardiology, neuroscience and endocrinology. UMH has the

prestige, the specialized personnel and access to state-of-the-art technology that such initiatives require.

Weaknesses: The obvious weaknesses of UMH are in two general areas, viz. payer mix and competitive disadvantages. Patient mix analyses reveal preponderance of Medicare and Medicaid patients and up to 30 percent of non-paying patients. Referral of indigent patients from the Baltimore area is disproportionately concentrated at UMH. The Health Data Management Center report also reveals that privately insured patients are unlikely, on the whole, to choose UMH for hospital care. Thus, the facility consistently operates well below capacity, resulting in cost over-runs. The fact that UMH specializes in treating the severely ill also means that its unit costs tend to be higher than at competing community hospitals.

It is also important to recognize that UMH operates to some extent in the shadow of the Johns Hopkins Hospital. With its extraordinarily successful public relations efforts and the public awareness and recognition of its facilities, Hopkins exerts substantial drawing power from all areas of the state and beyond. Most of the special services that UMH might wish to provide can be equally well offered by Hopkins, and the public is more likely to recognize those at Hopkins. The Health Data Management Center report indicates that the Johns Hopkins Hospital enjoys a 50 percent margin of patient referral over UMH in the suburban areas of Baltimore. The geographical proximity of the two institutions heightens the competitive problem. *Until recently, public relations efforts were not emphasized at all by UMH.* At present, the institution's

executives have begun to recognize the importance of public relations in attracting patients, but there is still a large gap between the investment of the two institutions in such efforts.

Action Strategies: Strategic plans for UMH can be derived from situational analyses and these will vary in scope, cost and presumed effectiveness. Paramount among the long-term objectives is enhancement of referrals of privately insured patients to increase revenues. There are many potential strategies to accomplish this but, in the HDMC document, we discussed three general categories dealing with: physician referral patterns; medical services and facilities; and public relations.

Objective 1: To improve physician referral patterns

[1] Undertake analyses to identify and characterize Baltimore-area physicians who refer and do not refer patients to UMH by specialty; hospital affiliation; UMH training; office location; and categories of patients by payer class.

[2] Use the findings in [1] to conduct opinion surveys of referring and non-referring physicians, including recommendations from physicians on methods to increase UMH referrals.

[3] Assess present status of other hospital affiliations with UMH in attracting patients to UMH, and to consider new and modified agreements.

[4] Increase personal and professional conveniences for referring physicians, e.g. establishing a doctor's dining room; valet parking for attending physicians; partial underwriting of malpractice insurance for physicians at UMH; and establishing a computerized clinical information system at UMH and consider sharing it with affiliated community hospitals.

Objective 2: To offer additional services and facilities likely to attract privately insured and self-paying patients

[1] Conduct surveys on insured or paying patients hospitalized at UMH and identify their reasons for selecting UMH; problems encountered; the institution's image; recommendations for change; etc.
[2] Conduct surveys in targeted Baltimore-area communities to determine why potential insured or paying patients would or would not choose UMH if they require hospitalization in the future.
[3] Establish one or more freestanding private diagnostic clinics for insured or paying patients.
[4] Set up satellite clinics to include twenty-four hour emergency services and to serve as components of a health maintenance organization.
[5] Contract with industry to offer pre-employment and annual physical examinations of employees located in the Baltimore region.
[6] Add executive suites for prominent patients admitted to UMH.
[7] Fix the daily price of a private room marginally higher than that of a semi-private room.
[8] Improve UMH security in a manner that is both substantive and apparent, without being intrusive to the patients.
[9] Consider adding a plastic surgery service at UMH.
[10] Provide free or reduced rate parking to UMH patients and families at lots near subway stations.
[11] Provide appropriate entertainment for hospitalized children.
[12] Provide complimentary layettes to mothers of newborns, and other amenities to selected categories of paying patients.

Objective 3: To create a positive image of UMH in the community at large

[1] Increase the staff, budget and capabilities of the Public Relations Office to assure that UMH accomplishments receive sufficient media coverage.
[2] Concentrate the guest lectures of UMH faculty at those hospitals and communities, which are likely to refer paying or insured patients to UMH.
[3] Produce health and medical education programs for public broadcast and cable TV in the Maryland region under the UMH logo.
[4] Sponsor and adequately publicize fund-raising events for the benefit of UMH.
[5] Disseminate the UMH magazine more widely to physicians and others in communities likely to refer private or insured patients.
[6] Encourage further development of the "800" telephone number and listing of UMH services available to physicians and hospitals in the region.

Additional Strategies to consider:

The Health Data Management Center offers a number of additional strategies for University Hospital to consider, many of which are related to our development of clinical information systems to monitor hospital performance and costs:

[1] Create a computerized system for the rapid entry, retrieval and analysis of clinical and cost information on UMH patients.
[2] Utilize [1] to monitor length of stay, charges, morbidity and mortality rates for each clinical service and DRG.

[3] Utilize [1] to examine trends in hospital admissions by residential area, payer status, referring physician, clinical service and DRG.
[4] Develop a system to classify patients by severity of illness and clinical outcome.
[5] Apply operations research techniques to analyze the hospital's effectiveness in providing patient care, by clinical service and DRG.
[6] Apply operations research techniques to develop computerized systems for scheduling admissions, intramural referrals, outpatient visits, clinical examinations, laboratory tests and surgical procedures.
[7] Undertake economic analysis of the determinants of UMH revenues and losses.

Chapter Nineteen Summary

Assuring a Promising Future for Public Health

There are two possible future scenarios for our public health educational institutions. The first is a relentless qualitative decline, as all clinical background requirements for student admission to these graduate-level programs are eliminated; courses, seminars, and research projects emphasizing the etiology and pathogenesis of human diseases are minimized; and a preponderance of academic offerings are in nonclinical subjects indistinguishable from those available at hundreds of universities beyond medical schools. If no action is taken, more and more public health schools will be established on college campuses remote from medical schools, portending a growing and ominous perspective that public health is not even a medical science, and should not necessarily remain in close proximity to the other medical specialties.

The second possible future scenario, and our prime recommendation, is for medical and public health schools to establish and strongly promote Clinical Public Health (CPH) Departments as their center of education, practice, and research on human disease, its causes, and prevention. Developing these CPH Departments will revive the satisfaction and exhilaration of students pursuing careers in clinical medicine, by creating a unique learning environment for matriculating physicians and nurses, offering them a dramatic new curriculum and other opportunities to become

personally involved in meaningful engagement in biomedical research on human subjects and all other aspects of public health practice.

While the studies described in this book meet all underlying biostatistical criteria, biomedical research these days is increasingly ignoring the epidemiological elements that are indispensable in the proper design and interpretation of studies on human health and disease. A significant number of axiomatic principles are now widely disregarded, and even opposed by researchers ignorant of the basic epidemiologic postulates. Carefully selected controls are often necessary but are now being neglected, and the widespread acceptance without much debate of Big Data analysis techniques demonstrates that much of the reasoning behind the Flexner and Rockefeller reports a century ago has been forgotten.

Creating the CPH Departments for clinically trained physicians and nurses will ensure that their public health education takes place in a positive and pleasant manner, with the young trainees interacting full-time with clinically experienced faculty in and out of the classroom. Since all faculty members of CPH Departments will have strong interests in human health and disease, they will be sharing their lifetimes of professional and clinical expertise, as well as personal experiences, with students and colleagues every day. Conflicts between different categories of students, those fully prepared and those shopping for possible careers in an arena they know little about, will be much less likely to occur, or to disrupt the learning environment, than at present.

Our second major recommendation is that each CPH Department develop a Health Statistics Center offering fee-for-service analytical reports to federal, state, and local health

agencies and hospitals on a routine basis, as well as in emergency situations such as the COVID-19 pandemic. The Centers will provide a strong resource in academic medicine, to balance the more politically motivated views of governments and boards of directors. Equally important, the fees collected will stabilize the budgets of the CPH departments and elevate their prestige and influence on and off campus.

CHAPTER NINETEEN

ASSURING A PROMISING FUTURE FOR PUBLIC HEALTH

AN AUSPICIOUS BEGINNING

A bit more than a century ago, the training of physicians was devoted to diagnosing disease in individual patients and treating or preventing the consequences of illness with the meagerly available technologies then available. Research was usually carried out by individuals without support from their medical schools, although the primordial biomedical research institutes in Europe were beginning to blossom. Public health practice and epidemiological research on the risk factors of disease were not even part of the curriculum of most medical schools. The Johns Hopkins Hospital and Medical School, inaugurated in 1889, was a unique exception. While emulating the style and substance of the foremost German and French biomedical research institutes, Hopkins also served as a theoretical model for the Flexner Foundation critique of American medicine.

The Flexner Report of 1910 criticized American medical schools for ignoring major dilemmas in the world's health, and for devoting insufficient effort to improving the quality of medical education and clinical training. At that time, medical schools had very few professors of public health, though progress in this respect was beginning to emerge in some of the European universities.

The Rockefeller Foundation became aware of the major shortcomings of public health training from the Flexner Report, leading to its decision in 1916 to endow the establishment of a new academic entity, graduate-level public health schools, on the campuses of the Johns Hopkins and Harvard Medical Schools. The rationale was to seriously address long-ignored dilemmas of public health without complicating the existing plights of the medical schools. It was decided not to add any new departments to the medical schools, but to build adjoining facilities for public health nearby. That this solution was inadequate is reflected in the vigorous growth of Public Health Departments in most medical schools a few years thereafter.

Physicians with public health experience were appointed as the principal faculty of the newly created public health and medical school departments of public health and recent medical school graduates who had completed their clinical training were the favored students. Doctoral-level biostatisticians also joined the faculty of these departments, as did experts in ancillary branches of public health such as health economics, environmental sanitation, healthcare administration, genetics, and population health.

In those years, bacterial, rickettsial, and viral infections were a deadly scourge of humans in many countries, and worldwide efforts to develop vaccines and advance our understanding of the pathogenesis of microbiological diseases and epidemics were undergoing major investigations in Germany and France, while just beginning in the United States. Malaria, yellow fever, and hookworm were among the central foci of the research and public health effort.

Publication and discussion of the Flexner Report and the Rockefeller endowment marked the onset of what came to be widely regarded as a Golden Age in medicine and public health. A host of shortcomings in medical education began to be addressed, though decades would be required for their resolution. Admission standards for medical students were formulated, although quotas for ethnic, religious, and diverse minority applicants persisted, and remain an unresolved problem. Course offerings began to meet recommended standards, and procedures for dealing with failing students were being established. Medical science was linked more closely to clinical practice, and students aiming for careers in teaching and research were beginning to be guided by faculty mentors devoting serious time to such responsibilities.

The two endowed public health schools began to address some of the urgent public health needs ignored by the medical schools of that era: promoting research on critical aspects of disease and fostering more effective public health practices to deal with the largely uncontrolled microbiological infections then affecting populations in all regions of the world.

Over the ensuing half-century, the public health schools grew in number and productivity, as did their medical school counterparts, the departments of public health and preventive medicine. Both of these types of clinical institutions underwent spectacular growth in attracting students, engaging in biomedical research, and achieving worldwide recognition of public health as an essential branch of medicine. They offered a broad diversity of courses in epidemiology, biostatistics, public health, healthcare management, environmental sanitation, and genetics, inter alia, and awarded master and doctoral degrees to their graduates. During these initial decades, the public health programs attracted

substantial numbers of clinically trained physicians and nurses enrolling to acquire the basic skills of epidemiological research, as well as a deeper understanding of public health issues and practices in the United States and abroad. The faculties of these programs were usually led by physicians who had received their public health training at one of the newly established public health schools, medical school public health or preventive medicine departments, or at the US Public Health Service, the Centers for Disease Control, and other federal health agencies.

During the early decades of the Golden Age in public health, faculty positions and deanships were commonly held by physicians with strong backgrounds in public health practice or research, and their investigations usually matched the high standards of clinical and biomedical science being practiced in the medical schools. The courses and seminars offered, as well as the mandated student research, were designed to meet the needs of students matriculating after completing their medical and nursing education as well as postdoctoral years of clinical training.

It should be borne in mind that, in those years, entrance requirements for medical school usually included college-level courses in mathematics, biology, chemistry, and physics, requirements that no longer exist in most medical and public health schools. The learning environment was ideal for the clinically trained students and their faculty mentors. It was also compatible with public health schools and public health departments thriving in a medical-school-dominated environment, thus minimizing pettiness, jealousies, and other negative relationships between students of diverse educational backgrounds and career interests. Such negative attitudes gradually became more evident in later years, when new

admission standards encouraged the enrollment of students with little or no medical or nursing background, thus opening a clumsy gap between diverse categories of students and their career aspirations.

Research in the public health schools and medical school departments during the Golden Age was dominated by epidemiology-based and hypothesis-driven studies of infectious and chronic human diseases. The students' efforts usually began with extensive literature reviews of the subjects chosen, formulation of potential hypotheses and development of study designs, followed by patient interviews, sampling of blood, urine, and other tissues for determination of infectious status, and, when required, X-rays, Papanicolau testing, and other biomedical procedures. Programs in water and air pollution, population genetics, and other significant ancillary activities of public health practice also flourished during this period.

Within a quarter-century of the Flexner Report and the Rockefeller endowment, American medical and public health schools had become the leaders of biomedical education and research in the Western world. While the basic scientists, engineers, and other technically trained specialists in these institutions studied viral diseases, developed vaccines, purified water, sanitized the environment, and explored the roles of insects and genes in human disease at the basic science level, their epidemiologically trained public health colleagues identified major risk factors of disease, such as cholesterol, salt, cigarette smoke, and asbestos, inter alia, tracked them throughout the world, and mounted risk-factor-based studies of human disease associated with them. A number of such studies undertaken by our team during this period are described in this volume.

The lingua franca adopted by most public health schools and departments during this era was epidemiology, a method of scientific reasoning beyond statistics that is uniquely appropriate to investigating risk factors of disease in human populations. The clinician-epidemiologists—i.e. those knowledgeable in the basic science of medicine, experienced in clinical practice, and trained in epidemiological studies of human health and disease—were the medical generalists at their public health school or medical school department of public health as they investigated the clinically observable but often ignored epidemiologic aspects of their disease of interest. Their colleagues—the PhD-level doctoral scientists engaged in molecular studies of genome arrays, amino acids, and other microscopic elements involved in human health and disease—were the researchers studying the micro-dimensional and basic science aspects of human disease. The latter investigators largely utilized animal models, rather than human patients, as analogues of their disease of interest.

DEPARTMENTAL SUCCESS

Our own Public Health Department greatly benefited from its location in Baltimore, the relative adequacy of funding, the politically neutral environment of the School of Medicine, and the highly supportive attitudes of most of the state's hospitals, physicians, patients, and politicians long before the full impact of enhanced federal regulations on human research began to take effect. We usually succeeded in gaining hospital approval for our studies, very few physicians ever refused to participate, and the patients and their families were almost always cooperative. These positive attitudes towards human epidemiological research were the result of a long history of warm, productive, and open relationships between our medical school, the hospital, and physicians on one side, and

the patients and families on the other. The diversity of studies undertaken by our public health faculty was rarely attempted by other public health school or medical school departments, in part because of the absence of the Baltimore-style tradition of supporting human disease studies, and in part because of the lack of departmental or school-wide leadership.

Much credit for the success of our studies on human disease was attributable to the staff nurses and aides the department recruited, individuals who were generally pleasant, knowledgeable, and firm believers in the medical and societal benefits of our studies, for both patients and society in general. They, the researchers, the clinical faculty, and the general public all seemed to share a common belief in the value of studying the risk factors and pathogenesis of the human diseases under investigation. This rationale was continually reinforced by departmental seminars on the clinical research, which were attended by clinicians and researchers from multiple departments. The seminars, in turn, often led to opportunities for new studies involving a diversity of participants from within and beyond the medical school. Complaints from patients and hospitals were extremely rare, and were largely dealt with by personal visits of the higher-level staff to the complainants.

Our studies frequently demonstrated the broad gamut of the epidemiological approach, as well as the benefits of interdepartmental cooperation. Among these was an investigation, agreed to by faculty dermatologists and family physicians, to compare the costs and quality of treating comparable patients by the two specialties, and a paired study of sexually transmitted HSV-2 antibodies in cloistered nuns and their married sisters (Chapters 13 and 9). Over time, many of our studies came to be regarded as “undoable” by the

mainstream public health institutions that had lost most of their clinically trained students and were increasingly intimidated by the expansion of governmental controls over the conduct of human studies.

As the number and scope of epidemiological studies in human disease declined, our department undertook a series of projects involving computer technology, which we anticipated would encourage Public Health Departments in medical schools to compete with commercial firms then dominating the development of institutional healthcare analyses required by all hospitals and medical schools (Chapters 11 to 18). Our unique rapid-reporting Maryland Cancer Registry became an overnight success, until, regrettably, political opposition transferred its governance from the university to a political body under total control of the state government (Chapter 10). Another pioneering effort undertaken with financial support from the American Academy of Dermatology was the first objective comparison of patient outcomes treated by two competing medical specialties (Chapter 13). Chronic suspicions arose between the two clinical specialties, which had never before agreed to objective evaluation, and terminated the study after a year, but the effort was a clear precedent for continuing such comparative studies in the future.

These and other efforts to extend epidemiological methods into previously ignored arenas of public health were quite successful, although more time and effort devoted to their political and public relations might have assured longer lasting outcomes. The Clinical Public Health (CPH) Departments that we strongly recommend in the future would strengthen the acceptance and durability of such new ventures, as the new departments increase their influence in medicine through multidisciplinary research and the revenues

they generate through fee-based short courses for journalists, lawyers, and business, as well as administrative analyses for hospitals and medical schools.

For readers to better understand our basic message, it would be useful to describe the prevailing spirit that animated the two public health schools funded by the Rockefeller Foundation during the Golden Age. Student selection for the graduate programs in public health at Johns Hopkins and Harvard Universities admitted a few dozen physicians each year who had completed their clinical training and were registered to practice medicine. Their professional and career interests were oriented around epidemiological research and public health practice. Conversations among them frequently dealt with recently published medical discoveries, as well as unpublished findings of research underway at their institutions. Discussions concerning career goals in public health were also stimulated.

The relatively small number of clinically trained physicians and nurses in the class, their common educational background, and their strong interest in public health careers created an environment in which even introverted students felt comfortable participating in discussions with classmates and faculty in class, during seminars, at lunchtime, and at odd moments throughout the workday. The medical libraries of both universities were very busy in those years, with students and faculty scanning the medical news every morning or evening, preparing theses, and reading publications on risk factors and other fundamentals of disease in humans. This atmosphere contrasts sharply with that in the public health schools a generation later, when physicians and clinically experienced students had become an insignificant minority, and courses were modified to meet the needs of the majority

of matriculants who had little knowledge or practical experience with bioscience or clinical medicine.

In undertaking their assigned research activities during the Golden Age, students augmented their own learning in the classroom with readings in the library, conversations with faculty, and interactions with their fellow students to augment their own formal learning. The student was the dominant figure in choosing the research topic, reviewing the existing literature, outlining the proposed study, and undertaking most of the labor to complete and publish the project. This contrasts with the more recent practice of students adopting a mentor's research interest over their own, and the complications arising therefrom. When the typical student completed a doctoral project in the Golden Age, he understood that this was his research from beginning to end. He could defend the findings and discuss the next investigational effort openly as a matter of pride, rather than to begin negotiating with a mentor's willingness to participate. Such experiences greatly raised the confidence of most students in entering the academic world of medicine and public health.

A FALTERING IN PROGRESS

The remarkable advances in public health began to falter in the 1980s, when a phenomenal new era was being welcomed by most elements in society, including its social, scientific, and business sectors. Young and old, black and white, males and females, all hailed the computer's multifaceted potential in their lives. At the very same time, however, dramatic changes were taking place in fundamental sectors of medicine and public health. Researchers were turning away from exploring the traditional agents, hosts, and environments of human disease in favor of pursuing a single all-important

target: the role of genes that are ultimately responsible for health and disease. Professors began to teach that epidemiology-based investigations, involving careful selection of human subjects and laborious medical literature reviews, were too complicated and time-consuming. The spectacular capabilities of computers to process billions of binary digits permitted these machines to replace much investigator input in human research, encouraged the universities to develop "Big Data" analytic methods free of much human decision making, and encouraged hospitals and physicians to prematurely promise patients (within legal limits) genetic cures of their disease.

Admission requirements for students in public health and medical schools were eliminated during this decade, the traditional epidemiology-based curriculum was watered down, and the faculties markedly reduced their interest in clinical studies of human disease. The advent of the new computer-based research technologies, and a massive increase in federal, state, and local rules and regulations governing human health research, all contributed heavily to the ebbing of interest and near-disappearance of risk factor studies in human subjects.

These developments reduced the interest of clinically trained physicians and nurses in classical public health careers and their replacement in the public health schools by applicants lacking knowledge or training in all or most aspects of human disease. The trend was accelerated by the explosive growth of the computer revolution and its medical consequence, the genome revolution, which rapidly captured medical interest and support throughout the bioscientific world. The evolution of high-speed computing became an open invitation for geneticists and computer specialists to concentrate their

efforts on rapidly decoding genome assays and ignoring the classical agent/host/environment approaches to disclosing the ultimate causes of human disease.

The loss of interest in traditional public health research careers by physicians, and their replacement in the public health and medical schools by matriculants lacking knowledge or training in human disease, now defines the status quo. Progress in genome assay methods has identified potential causal genes for a few human diseases, leading to reinforcement of the view among many public health and medical school faculties that traditional epidemiological studies and the need for careful attention to selecting appropriate control patients in studies were no longer necessary. The computer, and the unexpected popularity of its offspring, the Big Data analytical techniques, have been deemed adequate to replace the time, money, and commitment of the more complex desiderata of the traditional epidemiologic mode of studying human disease.

After the mandate for a curriculum matching the needs and interests of clinically trained students was deemed unnecessary, the public health schools and departments expanded their nonclinical course offerings and eventually permitted the admission of students without any background in medicine or clinical research. The end result was that traditional epidemiology-based courses and investigations in human subjects were increasingly ignored, while ancillary topics not based on medical knowledge became the prime interest of most students and faculty. Public health research became far more interested in counting and tabulating diseases around the world, than in investigating their etiology and means of prevention. Genetic research on animal and human genetic arrays continued as a most popular arena for

the laboratory-oriented scientists, while a new consensus arose among public health and medical faculties that traditional epidemiologic studies focused on agent, host, and environment, and careful attention to the selection of appropriate controls, were no longer necessary.

The time and effort previously devoted to identifying potential risk factors exclusive of genes has become a rarity. As a consequence, the computer and the newly developed statistical offshoots of the Big Data methodologies are now regarded as adequate to replace the faculty's time, money, and commitment to the relatively complex desiderata of traditional epidemiologic study. The simplicity of conducting much of the genome assay research now underway, and the host of clinically untrained students eager to enroll in its study, has never been challenged by the medical and public health schools. The latter seem far more interested in attracting rising tuitions from youngsters looking for careers, than in addressing the decline in meaningful research on human disease.

A plethora of studies on diversity in public health has accompanied the extravagant increase in regulations governing human health studies. The latter require little academic training in public health, or medicine but greatly increase the number of administrative positions sought by federal and state governments, as well as private firms.

MOVING TO A CAMPUS SETTING?

Another phenomenon of potential danger to the future of public health has recently become manifest. The location of public health schools within a university medical center is no longer considered important to its mission by some university

and governmental officials. For example, despite an outstanding record and widespread reputation of excellence in public health teaching and research over decades of time, the University of Maryland—the nation's first public medical school and hospital—has established a public health school at its campus in College Park, an hour's drive from its Department of Public Health at the medical school. This has already begun to lessen educational and research ties with the medical school in Baltimore.

It is reasonable to ask whether a college campus is likely to have sufficient patients and faculty comparable to those we were so successfully utilizing in our Baltimore program. The University of California has a public health school in Berkeley, though its hospital is multiple miles away in San Francisco. Other public health schools are considering similar moves, perhaps encouraged by heightened tuition revenues expected from college students seeking careers remote from human disease. The dispersion of public health programs from patients with disease to vague topics like diversity suggests that proximity to, and interaction with, a medical school is deemed no longer necessary in certain quarters. It is demoralizing for many of us to consider that academic programs in public health might become just another college major, rather than an attractive and demanding career of public service requiring medical training and clinical experience before one is licensed and considered fully qualified to engage in biomedical research and teaching.

REWARDING PATIENTS TO BE STUDIED; AN ETHICAL DISTORTION IN MEDICAL RESEARCH?

A distortion of ethical views that denigrates public health and clinical medicine these days can be seen by anyone stopping

at a local coffee shop. Instead of selecting subjects with caution, a hallmark of human studies these days is that patients are paid cash for their participation. You are likely to find notices on the bulletin board concerning money and other rewards being offered to people with or without a particular disease, if they agree to participate in a research study. Similar proposals are seen in local newspapers, shopping malls, social media, universities, and many other locations for patients with certain diseases or conditions to serve as study subjects paid by the investigator. A generation ago, it would have been anathema for a medical or public health school to advertise for patients, let alone pay them. For lay viewers, this may seem to be nothing more than a benign business proposal designed to attract participants. The medical scientists engaging in these solicitations, and their associated hospitals and pharmaceutical firms, strongly support this method of assembling patients as a legitimate and effective mechanism. The truth, however, is that soliciting patients in this fashion was universally considered unprofessional and ethically questionable during the entire Golden Age of medicine. In the past, professors universally taught that patients and controls must be carefully selected—never self-selected—in order to truly represent a general population or some other target population. The reasons are directly derived from the core teachings of epidemiology, the Hippocratic Oath, and the Daily Prayer of Maimonides, which are no longer discussed in medical and public health schools, or adhered to in studies on human disease.

What is wrong with advertising for patients, paying them, or otherwise ignoring the epidemiological principle of carefully selecting representative patients and controls for study? I offer a few responses for the reader's consideration:

1. On what basis can a study's findings in patients who accept or reject money, or other rewards, be accepted or rejected? Does the reward stimulate honesty or dishonesty?
2. What objective criteria can be applied to distinguish between patients who participate voluntarily and those who accept payments?
3. Is there a statistical test that can differentiate between the voluntary and paid patients?
4. How can the representativeness and objectivity of patients be assured when they receive payment for their participation?
5. Is it possible to assign an individual truthfulness score to each patient response?
6. In view of the extreme heterogeneity of humans, is payment likely to reduce the odds of identifying valid risk factors of the disease being studied?
7. In studying patients who accept payments, can the issue ever be objectively studied?

TOO MUCH MONEY AND TOO MANY REGULATIONS

A major government policy affecting epidemiological research and teaching was activated midway during the first half-century of the Golden Age. This was the onset of extramural federal funding in the 1940s by the National Institutes of Health (NIH) for basic and human research by investigators at American medical and public health schools. Over the next few decades, the NIH and other programs grew spectacularly and, by 1990, their operating budget rose to 1% of the federal government's, accounting for more than half of the country's health research funding. Early during this period, epidemiological research on human subjects flourished, and physicians were applying in decent numbers for training at

medical school public health departments and public health schools. The progress began to slow after a widely publicized situation in 1964 at the Brooklyn Chronic Disease Hospital, in which a few patients were injected with HeLa cancer cells without their consent. This quickly led to NIH-mandated review boards and, eventually, to hundreds or perhaps thousands of new rules and regulations by federal and state governments imposing excessively rigid rules for conducting human studies. The deluge of new rules greatly diminished interest and enthusiasm in epidemiological studies, and eventually displaced them with thousands of animal-based studies and statistically simple-minded studies on the pathogenetic findings in human genome arrays.

Another major deterrent to epidemiological research and teaching was a consequence of the remarkable growth of multicenter studies and cooperative clinical trials beginning around 1970. These were funded by the NIH for academic researchers and by the pharmaceutical industry, but were the product of committees of faculty, disparately located, rather than the creation of a prime investigator in a medical center. This new career pathway offered thousands of applicants an array of attractive benefits, including job security and decent salaries in the absence of tenure regulations, without much specific responsibility for designing studies or conducting research. The job benefits fostered the development of many collaborative multicenter projects and clinical trials, while discouraging individual physicians from pursuing careers in classical university-based epidemiological teaching, and playing leading roles in designing and conducting research on human disease. It is rare to learn of brilliant studies originating in the politically sensitive meetings of multicenter research organizations, though many have survived for decades.

The host of laws and regulations enacted by federal, state, and local government agencies designed to "protect the public" from any adverse outcome of participation in human research has greatly reduced the number of human patients available for study, as well as stifled the interest of investigators in continuing traditional epidemiological studies of human disease. Efforts to resolve these issues by political compromise and reasonable modifications in research procedures have been remarkably unsuccessful to date.

MENTORING OF PUBLIC HEALTH STUDENTS

Mentoring of graduate students has become problematical in many public health and medical schools, as a result of the academic downgrading of the public health programs. During the Golden Age, the mentoring faculty were full-time members of their medical school or public health school. When such individuals were assigned to assist a graduate student in identifying an appropriate subject for a doctoral thesis, his or her responsibilities were always considered secondary to the student's. The mentor discussed possibilities, made suggestions, and assumed academic responsibility for the student's progress. But it was the student who made the ultimate decisions, decided on the thesis, and spent several years reviewing the existing knowledge, formulating the study's testable hypothesis, carrying out the research, and conducting the analysis.

Mentoring in the present era is very different to that in the past. In many institutions, the mentors are full-time members of a clinical department, rather than primarily members of the epidemiological faculty in the medical or public health school. The academic interests of such individuals are usually in a narrowly defined medical specialty and rarely in public

health. Their long-term concern with mentoring is not designed to foster public health, but rather to secure assistance for the analysis of their own studies, and to help establish their reputations as epidemiologists, though often without undergoing much relevant training.

Because so many of today's mentors are primarily clinicians or basic scientists, rather than full-time epidemiologic faculty in a public health or medical school, their mentees are not as free as their Golden Age predecessors to choose thesis topics of prime interest to themselves and their career objectives. Instead, an agreement must be reached between mentor and mentee on the study's purpose, methodological details, and analysis, which thus limits the mentee's involvement and potentially creates conflicts with the mentor. Realistically, the thesis becomes just another of the mentor's projects, in which the mentee participates but does not dominate. In no way does this permit the student to assume traditional responsibilities for independently designing a thesis, carrying out the research, and conducting the analysis.

Problems constantly arise when a student desires to modify the research project in a fashion that falls outside the mentor's long-term interests. When the mentor is not a full-time member of a public health or medical school epidemiology department, disputes of this kind can be very disruptive. Three basic issues are of major concern here:

1. **Who designs and owns the thesis?** Mentors nowadays often assign students projects that were basically developed by the mentors, and about which they are reluctant to permit modifications that primarily benefit the student.

2. **Mentors for public health students in the past were usually full-time members of the Public Health Department.** Today, most mentors are members of clinical departments, permitting much less oversight and academic supervision by the public health faculty.

3. **Theses cannot be modified without the mentor's approval, which thus discourages students from seeking a possible replacement and creates groups of permanently dissatisfied students at their schools.**

All of these issues tend to isolate the students at a critical time in the development of their thesis or first paper. Revisions in the regulations concerning mentors, students, and their interactions are a major problem in need of discussion and resolution.

CENTRALIZED VERSUS DISPERSED MEDICAL CARE AND EDUCATION

During my own medical training, and for many decades thereafter, it was widely taught that medical care should be as centralized as possible in order to accommodate the patients' physical limitations and personal convenience as well as the medical practice. Another significant benefit of such an arrangement is that the knowledge base of most physicians attending such clinics is gradually broadened and deepened, as is also true for the students in training. When medical practitioners in diverse fields practice close to one another, they are likely to confer, chat, and absorb clinically useful facts about their neighbor's specialty as well as their own. While serving as an Assistant in Medicine at the Peter Bent Brigham Hospital, I benefited greatly from the same phenomenon, as there were always specialists in the clinics

representing other specialties than my own. However, as the medical campuses began to radiate outwards, this format of practice began to disappear. If you are training in dermatology at Stanford, for example, your service may now be remotely located from the central hospital, and your opportunities to interact with other clinical specialties are reduced.

The rationale of the widely dispersed medical care system today is primarily financial. Those managing hospital budgets are overwhelmingly concerned with competition from local and even national systems, established solely on their likelihood of profit and loss. Many of the well-established features of traditional clinical diagnosis and medical care are constantly compromised in favor of the dollar and the bottom line. The hospital leaderships usually think in terms of three possibilities: expanding by absorbing competing systems; joining an existing competing system; and closing down. Only a handful of experts nowadays consider less disruptive alternatives such as: pursuing excellence at their hospital while neglecting a few costly specialties; adapting telemedicine and other modern techniques to compensate for their limitations; and—most importantly—maintaining a directorate and staff that is totally devoted to their hospital, rather than buying out, or being bought out by, the competition.

Students and trainees learn much from discussing and considering the experiences and views of their colleagues and faculty, even those in rare clinical specialties. Like many other subjects, epidemiology and its applications are a medical specialty best learned by congregating students and faculty in classrooms and laboratories for discussion and debate, not by dispersing individual students to spend an hour or two with busy practitioners far from the medical center.

Despite the clear-cut advantages of centralized medical care and education, current trends are moving in the opposite direction. Stanford Medical School has recently built a $2-billion hospital on its campus while, at the same time, establishing major clinical facilities up to half an hour or more away in Redwood City, San Jose or other locations. Branches of the University of California medical system compete with Stanford in the latter's immediate vicinity. This Wild-West type of competition occurs in much of the country, resulting in centralized medical care losing its innate advantages for patients, physicians, and public health trainees.

GLAMOR VERSUS REALITY IN PUBLIC HEALTH

Flocks of college graduates in search of careers succumb to the almost irresistible recruitment propaganda of public health schools and departments of public health. Glamorous descriptions of work involving trips to scenic sites in exotic Africa and Asia are very enticing to young people, especially when so little is demanded of them in return. With minimal effort, they can earn a master's degree in public health, despite serious deficiencies in their knowledge of human disease, its pathogenesis, treatments, and control. After a year or two of public health schooling, the graduates will usually accept positions in government agencies or private institutions, where they are put to work counting populations at risk of disease, but they will never be able to mount, or even evaluate, the simplest studies concerning a disease or how to cure, treat, or study it. The public health education of these students will have consisted of introductory-level courses in health economics, women's health, minority health, healthcare management, diversity, and other subjects that can be pursued at most college campuses around the country, and usually at much lower cost. From the perspective of the public

health schools themselves, however, there is a growing realization that such students have become a major source of revenue for the university, achieved by downgrading their programs for qualified physicians and nurses with interest and expertise in clinical training.

THE END OF AN ERA

The developments described above gradually brought the Golden Age in public health to an end. One consequence was that epidemiological studies—the fundamental research mode in public health—have become so difficult to organize, that they are now almost absent from the medical armamentarium. In its place are innumerable computer-based searches for genomes arrays that might theoretically contribute to a human disease. While useful findings do occasionally result from such research, much of its popularity is based on a built-in statistical technology that draws conclusions without much input from the investigator. The Era of Big Data, and the absence of carefully formulated scientific hypotheses, seems to be upon us.

Careers in epidemiology-based education and research are no longer viewed as attractive career options for many young physicians with strong interests in academic medicine or public service. Faculty members of public health schools and departments have been discouraging the classical epidemiological approach to research for decades, arguing that it is overly complicated for students or themselves to undertake. They recommend abandoning the challenges of exhaustive literature review, hypothesis formulation, and careful selection of controls for the diseased patients. Many investigators even utilize previously published data on patients participating in earlier studies as the basis for their

own so-called “new” research projects.

As the students and leadership of public health schools and departments of public health began shifting from physicians to non-physicians, and from clinicians to non-clinicians, the schools transformed their curriculum, degree requirements, and other criteria from programs designed for the medically sophisticated to those for the medically untrained. To ease this transition, survey courses in medicine were introduced to familiarize new students with medical terminology, and with the major categories of disease and disability. The approach proved widely unsuccessful and the usual trainees today still remain incapable of dealing with most problems in public health.

Public health schools and departments today are far from idyllic facilities for teaching and guiding the careers of students in the principles, methods, and potential solutions to the worldwide problems of public health. Creating an appropriate setting for such learning should begin by selecting a student body capable of mastering the epidemiologic principles underlying public health, addressing the array of health and disease issues of consequence, and maintaining a pleasant and effective environment for teaching, research, and public health practice programs.

Such optimal conditions are almost never present in today’s public health departments and schools of public health. The reality being confronted is that each class of students is hopelessly diverse in its academic background. A small minority may be clinically trained physicians or nurses with a genuine passion to become educators, researchers, or practitioners of public health. Most of the others matriculate without any formal knowledge or experience in human health

or disease, but are simply harboring an interest in exploring potential aspirations for job careers in the healthcare industry. If successful, they will enjoy the salaries and other benefits of their jobs, but will never experience the joys of teaching committed students or advancing public health.

The diversity existing in the educational backgrounds of today's public health students renders it very difficult for academic departments to develop programs addressing the unmet health needs of the public as a whole. Medical and public health schools have prepared overview courses in introductory medicine that proved meaningless to the clinically trained students, and that failed to prepare the unprepared trainees for tackling serious problems in public health. This dilemma sometimes promoted ill feelings between the two categories of students, or the failure to create academic programs that were informative to all matriculants. A year or two in such environments rarely boosted student enthusiasm or competence in preparing for lifetime careers in public health.

A growing weakness in today's public health programs is their failure to undertake epidemiological studies of identifiable agents, hosts, or environmental risk factors in human disease. Far more popular among faculties today is the statistical testing of genome arrays purchased from commercial companies for their possible role in disease pathogenesis, an approach that is often far less illuminating than classical epidemiologic studies. A common doctoral thesis today involves statistical tracking, i.e. tabulating time trends in disease prevalence and mortality by sex or ethnicity, rather than identifying potential causes of disease and modes of prevention or treatment. This approach is much less likely to yield useful results, even though the studies described in this

book were all successfully completed without harm to the patients, and with valuable information afforded the medical profession and society at large.

Another solemn sign of the times is the enormous effort now underway to improve the technical skills of faculty members in applying for research grants in medicine and public health. Most medical and public health schools sponsor courses designed to improve one's ability to apply for grants, and a variety of private and governmental agencies offer courses and sell manuals for this purpose. Individuals who never received research grants themselves often develop these programs, which thus renders their courses a summation of government regulations rather than a useful guide for improving grantsmanship. The situation differs widely from that in earlier eras, when young faculty were expected to write their own grants, based on their own medical interests, with secondary assistance from faculty mentors.

We have described above a typical student workday during the formative years of the public health schools. Let us now sketch a typical day during more recent times. Instead of a few dozen physicians, the classes are now much larger, consisting of a preponderance of students without medical training or, in fact, scientific knowledge of any aspect of human health or disease. Superficial courses in health and disease continue to be offered, but neither students nor faculty believe that they compensate for existing educational deficiencies. Over time, this has led to the near disappearance of epidemiology-based teaching and research, and a mass movement of students into newly created ancillary subjects such as health economics, genetics, healthcare management, and environmental sanitation, where deficiencies in medical knowledge are largely acceptable.

If there are physicians or nurses with clinical backgrounds in today's classes, there is little communication of educational value, and sometimes a tendency toward competitive antagonism, between those trained in health and the untrained. The courses in the ancillary subjects are certainly important for public health, but they cannot compensate for the near absence of authoritative lectures, seminars, and laboratory courses dealing with human health and disease. Furthermore, most of the ancillary subjects are now offered by hundreds of colleges and universities, from coast to coast, in addition to the medical and public health schools, while programs offering classical epidemiological training and research in depth on human disease are now very few.

During the Golden Age of medicine, educational and research activities in the public health schools and departments involved physicians who were paid full-time salaries, generated no clinical fees from patient care, and were based in the school's public health facility. Today, many public health physicians are based in clinical departments, earn clinical incomes, and still serve as public health professors and mentors. Their dichotomy of responsibilities creates potential conflicts between patient care responsibilities and academic duties in teaching and research in public health. Since the clinical fees generated by clinicians are a critical income source for medical schools and teaching hospitals, monitoring their academic performance is sometimes considered secondary to their clinical income. Is there less interest in monitoring the academic performance of such physicians than in their clinical activities? In a number of public health schools today, physicians are awarded public health degrees, and even permitted to use the title of epidemiologist, without having mastered much about this medical specialty or devoting substantial time to teaching and researching the subject.

The readers are urged to read some of the studies published by my colleagues and students during the past half-century. Despite the overwhelming influence of computerization, the disappearance of hypothesis formulation, and the popularity of Big Data analysis, these clinically trained epidemiologists have maintained the Rockefeller Foundation's original principles in their research and teaching. A few of their classical studies are noted here:

1. "Is diabetes mellitus a teratogen or a co-teratogen?" (McCarter, Kessler, and Comstock 1987, 195-205);
2. "Risk factors for male breast cancer" (Mabuchi, Bross, and Kessler 1985a, 371-375);
3. "Cigarette smoking and nasopharyngeal carcinoma" (Mabuchi, Bross, and Kessler 1985b, 134-136);
4. "An epidemiologic perspective on ovarian cancer" (Lin and Kessler 1980, 1-17);
5. "A multifactorial model for pancreatic cancer in man" (Lin and Kessler 1981a, 147-152);
6. "Incidence of pancreatic cancer—Reply" (Lin and Kessler 1981b, 2575-2576);
7. "Epidemiology of cancer of the vulva: A case control study" (Mabuchi, Bross, and Kessler 1985c, 1843-1848); and
8. "Cancer risk in tuberculosis patients" (Mabuchi and Kessler 1983, 363-374).

ASSURING THE PROMISING FUTURE OF PUBLIC HEALTH

To address the serious issues described in this chapter, there is an urgent need to establish autonomous Clinical Public Health (CPH) Departments for physicians and nurses in selected public health and medical schools. These would eventually

function as each school's center for clinically oriented teaching and research on human health and disease. The CPH Departments should be physically separate from the other academic divisions that accept students lacking clinical or health backgrounds. Their matriculating physicians and nurses can also enroll in their school's existing courses in health economics, healthcare policy, environmental health, genetics, and other ancillary subjects, but most of their time must be devoted to learning, fraternizing, researching and dining with their clinically trained classmates and faculty mentors.

Public health is now increasingly being viewed as separate from, or not directly linked to, medicine. Such developments bespeak the need to strengthen the medical, clinical, and political capabilities of the public health schools and medical school public health departments, if public health is to survive as a significant branch of medicine, and remain a significant movement in the quest for valid risk factors of human disease and the practice of preventive medicine and public health.

Only a few public health schools and preventive medicine departments still maintain programs to train physicians and nurses in the design, conduct, and analysis of epidemiologically based studies of human disease and its causes, treatments, and preventatives. An extravagance of efforts, resources, and funds are now being devoted to genome research at the same time that a host of potentially significant epidemiological discoveries hidden in man's constitution, environment, diet, and behavior remain undetected and unsearched for. The changes we recommend will resurrect academic excitement among medically trained students and nurses, many of whom will begin to seriously consider aiming for leadership roles in public health education, practice, and clinically relevant research.

Public health institutions must remain in or close to the medical centers in which their faculties work. While many faculty members from other clinical departments often accept joint appointments to a public health school or medical school department pro forma, this rarely enhances the viability or academic productivity of the school's public health roles. Our recommendations would foster much closer educational and research relationships between the CPH program in the public health or medical school and the clinical departments.

At present, only a handful of departments in medical and public health schools nationwide possess the characteristics essential for their transformation into CPH centers as proposed here. These are the schools that could theoretically attract clinically oriented faculty and students into the new program as quickly and smoothly as possible. They would also need to prepare themselves for the newly emerging theories that now challenge epidemiology, such as the Big Data methodologies and the statistics-based analytical centers being established at Harvard (Harvard Magazine 2014). These, and other minimizers of epidemiology-based teaching and research, will pose dangers to the future of public health for years to come.

GENERAL DETAILS OF OUR RECOMMENDATIONS

Establishing CPH Departments in carefully selected preventive medicine departments and public health schools to further train cadres of doctors and nurses with substantial clinical experience and appropriate career interests is our principal recommendation. While the existing public health programs could continue to educate students lacking medical backgrounds, the new CPH Departments would aim at becoming the primary pathway for educating physicians and registered

nurses to assume leadership roles in public health education, clinical practice, and epidemiology-based research in public health. After decades of attending to the needs of matriculants with little or no background in medicine, the public health institutions would once again be emboldened to resume their unique role in advancing knowledge and training public health practitioners for the benefit of mankind. The world will rejoice to see hundreds of young physicians and nurses attracted each year to prepare themselves for careers in public health education, public health practice, and research on the causes of human disease and disability.

This recommendation will go far in rectifying the current shortage of public health physicians and nurses whose medical knowledge and clinical experience must be reinvigorated for their increasingly significant roles in the future. The problem, as described earlier in this book, resulted from a downgrading of the public health curriculum to accommodate the needs of the nonclinical majority of students then being admitted to the public health institutions. Establishing a cadre of clinically proficient faculty, and attracting clinically experienced student bodies into CPH Departments, need not have a negative impact on existing programs for nonclinical students, which can continue in their own separate facility.

The benefits of developing faculties of CPH Departments—attracting clinically trained physicians and nurses as students, and enhancing educational, research, and career emphases on clinical diseases rather than social and economic conditions of society—could be rather quickly realized in a few new CPH Departments. The programs would excite the interest and activate clinically trained students with serious career interests in public health practice, teaching, and epidemiological

research on human disease. The presence on campus of a clinically oriented faculty scheduling seminars on their own research would also stimulate positive reactions among most of the other medical school departments, another highly desirable achievement.

Examples of the clinical research agenda we recommend can be found among the examples of our own studies that are described in this volume (Chapters 3 to 18). Cancer risk among diabetics, the roles of melanin and nicotine in Parkinson's disease, and the history of artificial sweeteners in bladder cancer are as relevant to public health practice today, as they were decades ago. The unique characteristics of the HSV-2 virus as a probable causal agent for cervical cancer, and the classic epidemiologic research performed to prove it, remain wonderful teaching tools even though the Nobel Commission mistakenly awarded its prize for HPV, as the cause of cervical cancer. Since that time, the disease has shown little relationship to HPV, while the evidence on HSV-2 remains strong, though incomplete The real life consequences of governmental decrees "to protect the public" from participating as research subjects is evident from the diethylstilbestrol and vaginal cancer controversy, and solid epidemiologic research can continue to be carried out in difficult settings such as with cloistered nuns and their married sisters. The urgent need for objective comparisons of clinical care was awakened by our research (Chapter 13), but must be continued, and the leadership of clinically trained epidemiologists continues to be essential in all such efforts, now and in the future.

The clinical departments in some medical schools could also begin to utilize the epidemiological, statistical, and computer resources of a CPH Department in their own research and

teaching programs. And, eventually, clinical students from these clinical departments might enroll in courses, and participate in seminars, offered by the CPH faculty. Another beneficial outcome would be a gradual improvement in the somewhat distant relationships now apparent between public health students immersed in social science and their medically oriented fellows concerned with disease pathogenesis and control.

Harvard University recently announced plans to develop a university-wide program in data science, beginning with construction of a central facility adjacent to their engineering and applied sciences school in Allston, Massachusetts. Three master's degree programs in data science are being launched in medicine, public health, and arts and sciences. The program's leaders are headed by a dean for computer science and a professor of statistics at the School of Public Health, which clearly identifies the program as being dominated by statisticians and computers, rather than by classical epidemiologists/physicians in pursuit of agents, hosts, and environments of disease (Shaw, 2014, 30-35).

The rationale for the new Harvard program, in their own words, is that "data science is central to research in public health, the physical, social and biological sciences and medicine". In a companion article to the announcement, it is revealed that a fundamental target of the program is to utilize Big Data methodology to understand how six billion base pairs of the human genome affect human health and disease. This approach contrasts starkly with traditional hypothesis testing, in which the investigator, usually highly knowledgeable about the disease in question, carefully searches the medical literature to identify unknown risk factors, and proceeds to subject them and his own presumptions to meticulous investigation.

Articles published lately point out that only a tiny fraction of the human genome has yet been studied with much intensity, and that only a minute proportion of human diseases have yet been clearly linked to specific gene arrays. We would estimate that fundamental progress in understanding the pathogenesis of most cancers and other serious diseases is years or decades away. This argues strongly for strengthening and increasing the number of epidemiologically based studies of causal factors in human disease, the principal alternative approach to genetic research. Much more funding will be needed for this, of course, but the critical issue is how to entice a large enough body of young clinicians with the required talents to opt for this type of research in their careers. The establishment of CPH Departments in medical and public health schools is heavily based on this mode of reasoning.

Both types of human biomedical research analysis can lead to new knowledge or fail in their quest. The Big Data technique takes advantage of the current success of advanced level computing to search through millions or billions of data bits for genomic elements associated with a disease in question. The traditional epidemiological technique relies on individual investigators identifying specific human characteristics or biomedical traits of study subjects that differentiate them from control patients, and may be related to their genotype and disease causality.

Sir Isaac Newton's theory of how light is deflected by the sun's gravity could not be tested until three centuries after his death. The world had to wait until Einstein's general theory of relativity was proven before determining that a total solar eclipse in 1919 would allow telescopes to measure the curvature of starlight passing through the rim of a darkened solar disk. Similarly, sufficient time and future biomedical

discoveries must occur before we fully understand how they interact to produce health and cause disease.

As we have noted, spectacular advances in computer technology made Big Data analysis possible, which is a trend that will continue, as demonstrated by Harvard's data science initiative and reports from other universities (Harvard Magazine 2014). But abandoning classical epidemiological research, the alternative to genotype research and hypothesis-free computing, can quickly lead to deleterious effects on the nation's future healthcare.

SUMMARY OF OUR RECOMMENDATIONS

Objective One: Accredit and Establish a Training Program for Clinically Trained Physicians and Nurses in Public Health Practice and Epidemiological Research

Step 1: Hold informal meetings with interested medical or public health faculty members and students to discuss the proposal. If a positive consensus emerges, form a CPH Committee to formalize the process. Discussions with other department chairmen, students from various departments, and, eventually, deans of the medical or public health school would be scheduled next. Critical issues to be raised would include:

a) Can a CPH Department enhance career training in public health and epidemiology for doctors and nurses more effectively than existing programs?
b) Can the total cost of a CPH Department be significantly reduced through fee-based ventures, such as short courses in health and disease for journalists, lawyers, and business executives, as well as by offering

analytical services to government agencies, medical schools, and hospitals?

c) Is public health training on a medical school campus better suited for clinically proficient matriculants, than programs centered in university campuses remote from the hospitals and their medical and public health schools?

Step 2: After the CPH Department has been officially approved for the medical or public health school, selected faculty members will begin preparing the academic courses dealing with the epidemiological underpinnings of public health, and the methods for investigating the pathogenesis and control of disease in human subjects. This effort will be split among five groups of the faculty, according to their training and interests:

a) **Group One** will determine which courses and seminars offered by the original Public Health Department should be retained in the new curriculum, with or without modification. Decisions would include: major changes; minor changes; and no changes.
b) **Group Two** will decide on the new courses needed, and assign their development to CPH faculty and new faculty to be recruited.
c) **Group Three** will discuss seminar and conference presentations for students and faculty, mandatory or voluntary attendance, assignment of academic credit, and the development of new types of presentations designed to stimulate selected groups of students and faculty.
d) **Group Four** will develop and inaugurate the first series of epidemiologically based research ventures, long ignored by most medical and public health schools, i.e.

short courses in healthcare for journalists, lawyers, and the business community.

e) **Group Five** will interact with the university and medical school to determine their interest in having the CPH Department produce analytical reports periodically required by governmental agencies, hospital associations, and hospitals.

Step 3: A critical task of each CPH Department will be the formal recruitment of an enthusiastic clinically trained faculty with active public health interests in education, research, and public health practice. Generating favorable public relations and acquiring financial assistance from major foundations will play important roles in this step.

Step 4: Clinically oriented seminars, specifically designed to attract attendees from the other medical or public health school departments, will be developed by a group of active faculty. The intention is to stir the interest of students and faculty from the other departments, and help the CPH department to attract new students.

Step 5: Once the CPH Department has achieved a basic level of stability, it will begin to inaugurate a number of unique ventures that have never, to our knowledge, been undertaken by any other medical institution. These ventures are described in the following paragraphs below.

Objective Two, Unique Venture No. 1: Create a Health Statistics Center for the CPH Department.

This venture will become the department's fee-based agency for calculating, compiling, and informing the public of significant diseases affecting their regional population. One

objective would be to avoid recurrence of the statistical chaos associated with the COVID-19 pandemic. Another would continue the previously established cancer registration system designed for rapidly identifying all patients diagnosed with cancer, as close to its time of onset as possible. A third aim would extend the latter system for studying other diseases of interest.

The dynamic existence of an Agency with such analytical capabilities should be attractive to federal, state, and local governments, especially after their dismaying experience with COVID-19. The notion of *a truly science-based medical center objectively reporting on the region's health and disease will reassure the public that the government's decisions are being made on the basis of science rather than politics. The cost of establishing such a Health Statistics Center will be logarithmically lower than the government's disorganized spending on COVID-19 and other issues.*

Objective Three, Unique Venture No. 2; Develop a short course for journalists and journalism students to prepare them for careers in reporting on health and disease.

This initiative by the CPH Department would create a 6-month to 12-month educational program to upgrade the fundamental knowledge of journalists and journalism students who write about human health and disease. At present, good writing skills are regarded as a desirable asset for journalists. But what about their knowledge of healthcare, the subject about which they are reporting? It is currently estimated that nearly 20% of the US economy will be spent on healthcare by 2026! Does the present quality and depth of reporting on healthcare comport with its importance to the nation and the highest standards of journalism? Or is much of healthcare

news today largely echoing the views of the pharmaceutical industry, government, the hospitals, and other interested parties for whom the bottom line is sometimes financial and sometimes political, rather than the public's health?

The following steps would be required to initiate this venture by the CPH Department in a medical or public health school:

Step 1: The School and CPH Department would approve the development of a fee-based academic short course in health and disease for journalists and journalism students. The 6-month to 12-month program would prepare journalists with a solid introduction to health and disease that is presently unavailable elsewhere.

Step 2: A committee of CPH Department faculty, other medical school and journalism school faculty members, and a few experienced health journalists would be appointed to prepare, review, and finalize the short course in healthcare for journalists and journalism students.

Step 3: A few journalism school faculty, together with CPH faculty, would be invited to join the venture in conducting the short course, modifying it, if necessary, and overseeing its receptivity and effectiveness. A skilled individual to promote the short course among journalism schools, news media, academic institutions, and the general public would be recruited to promote the venture.

Step 4: The academic portion of the short course would include lectures and discussions on: human, animal, and genome studies in medical research; biological proofs vs. statistical proofs of causality; government-sponsored vs. corporate-sponsored research; critiques of healthcare

reporting in newspapers, magazines, television, and social media; and information sources for healthcare, including government, hospitals, healthcare industry, and medical journals.

Step 5: *Supervised weekly exposures to clinical care* in hospitals and clinics.

Step 6: *Supervised weekly exposures to laboratory medicine* and pathology.

Step 7: *Supervised weekly exposures to basic science and clinical research.*

Step 8: *Weekly meetings of students with faculty mentors and journalists* to review what they have learned.

Step 9: *Graduation, honors, and press interviews.*

Objective 4, Unique Venture No. 3: Develop a short course for lawyers and law school students to prepare them for roles as defense attorneys and prosecuting attorneys in healthcare and malpractice lawsuits.

Healthcare-related lawsuits were extremely rare in the first half of the 20th century. Today, malpractice premiums in the US are already approaching $60 billion annually! Strengthening the knowledge base and judgment skills of lawyers and law students in health and disease matters through this short course will substantially improve the quality of the legal community's actions in the legal aspects of healthcare.

Lawyers involved in healthcare often need help in understanding the fundamental aspects of health and disease, the types of

research on causal factors of disease in animal, human, and genome-based studies, and biological versus statistical proofs of causation. They will benefit greatly by analyzing case reports with health experts and experienced attorneys, in which legal judgments are justifiably or otherwise attributed to the workplace, government malfeasance, genetics, criminality, or other factors.

An example of innumerable breakdowns in what should be a rational and fair system for judging guilt or innocence in causing disease is the mesothelioma dilemma. Exposure to an indeterminate level of asbestos has been acknowledged as a cause of mesothelioma since the 1960s, although most individuals claiming such exposure do not develop the disease. Studies have revealed a number of other factors, such as genetics and cigarette smoking, that contribute to the risk and, eventually, asbestos bankruptcy trusts were established through government intervention to pay billions of dollars to affected patients. After the trust funds became available, hundreds of law firms were established to negotiate payouts to real and potential mesothelioma cases and their attorneys. Epidemiological research to refine our knowledge about which asbestos-exposed individuals succumb to mesothelioma has long ceased, but the payout of expenses and legal fees continues unabated, as is true for other diseases as well.

The urgent need to fill a growing gap in legal education and practice of healthcare law would be addressed by the CPH Department. The following steps would be required:

Step 1: A committee, consisting of CPH Department faculty, other medical school and law school faculty, and one or two experienced practicing attorneys would be appointed by the CPH Department to prepare, review, and finalize a short

course in healthcare for law students and lawyers.

Step 2: A small number of law school faculty would be invited to join with CPH Department faculty in conducting the short course, modifying it if necessary, and overseeing its receptivity and effectiveness. An individual to promote the short course among law schools, attorneys, the news media, and the general public would be recruited as part of an ongoing assessment of the venture.

Step 3: The principal academic portion of the short course offering would be a fee-based 6-month to 12-month course in "Epidemiology for the legal profession" to be created by the CPH Department in collaboration with other medical and law school faculty. It would include lectures and discussions: on human, animal, and genome studies in medical research; biological proofs vs. statistical proofs of causality; government-sponsored vs. corporate-sponsored research; critiques of healthcare reporting in newspapers, magazines, television, and social media; and information sources on healthcare, including government, hospitals, healthcare industry, and medical journals.

Step 4: *Supervised weekly exposures to clinical care in hospitals and clinics.*

Step 5: *Supervised weekly exposures to laboratory medicine and pathology.*

Step 6: *Supervised weekly exposures to basic science and clinical research.*

Step 7: *Weekly meetings of student with their faculty mentors and attorneys* to review what they have learned.

Step 8: *Graduation, honors, and press interviews*

If the program for attorneys is successful, the faculty could consider developing a modified short course for educating judges in healthcare, or combining it with the short course for attorneys. It should be noted that the idea of offering short courses to enhance expertise in law has already begun. At the University of Arizona College of Law, for example, students are now undergoing training in non-JD aspects of human resources, finance, education, compliance, and taxes, all of which are related to law.

Objective 5, Unique Venture No. 4: Develop a short course for business executives to prepare them for careers in the healthcare industry.

This initiative, a fee-based 3-month to 6-month venture, for business executives would be designed to introduce them to significant features of healthcare as a business and investment prospect. A key feature of healthcare in America is that it spends more as a percentage of GDP than most other countries, as a consequence of higher prices for services, higher costs for administration, and greater utilization of services.

The short course would include analysis of data from a clinical information system, like the one the department developed for dermatologists. This would undoubtedly disclose higher rates of misclassifications, diagnostic errors and losses due to pharmaceutical errors, duplications, and marginally defensible or indefensible hospital-based and home-based treatments. The CPH Departments could readily compete with the far more expensive commercial companies in offering such a course.

Research and development of pharmaceuticals and medical devices, which must be approved for use, are now a $60-billion annual business in the US, which is about 80% of the world's total. Healthcare services are increasingly directed at the older population, although the media often focus on the young, perhaps for emotional reasons. In recent decades, patient expenditures on alternative medicine have also grown substantially (now in excess of $30 billion per year), but are not covered by health insurance.

Healthcare is such a steep expense for the nation that it is regulated by an elaborate, costly, and imperfect federal and state system. Although many agencies and government bodies are legally responsible for quality assurance in healthcare, we are far from achieving a level of success and coverage that a nation as wealthy as ours deserves. The CPH Departments could play a very significant role in developing a national clinical information system that would eliminate waste, uncover fraud, serve the entire population, and regain our past leadership in healthcare.

The following steps, analogous to those for the journalist and lawyer ventures, would need to be taken:

Step 1: A faculty committee in the CPH Department, together with a few business school faculty, a lawyer, and an entrepreneur would be appointed to prepare the draft of a fee-based short course program in healthcare for business students and business school faculty, of about 3 to 6 months duration. Approval would be sought from the medical school and business school deans, as appropriate.

Step 2: A carefully chosen number of CPH Department and business school faculty would be selected to refine the draft of

the program and participate in offering the short course.

Step 3: The program would be a 3-month to 6-month course in the "Epidemiology of health and disease for business practice." It would include lectures on: animal, human, and genome studies in medical research; biological proofs vs. statistical proofs; government-sponsored vs. corporate-sponsored research; legal case reports on significant healthcare issues resolved in legitimate and political fashions; healthcare data sources including government, hospitals, healthcare industry, and medical journals; and discussions of healthcare as a national problem and how a national clinical information system would help resolve it. Seminar discussions of significant legal cases involving healthcare in a business would also be discussed.

Step 4: *Supervised weekly exposures to clinical care in hospitals and clinics.*

Step 5: *Supervised weekly exposures to laboratory medicine and pathology.*

Step 6: *Supervised weekly exposures to basic science and clinical research.*

Step 7: *Weekly meetings of students with faculty mentors and business school faculty* to review what they have learned.

Step 8: *Graduation ceremony, honors, and press interviews.*

Objective 6, Unique Venture No. 5: Prepare analytical reports needed by hospitals, medical schools, and government health agencies.

The CPH Department, while maintaining its academic teaching and research programs, could also satisfy the needs of medical schools, hospitals, and governmental obligations that have traditionally been delegated to commercial firms. This would save money for the client, reduce reliance on for-profit companies, and build closer relationships within the CPH Department. An example of the analyses would be the periodic assessment of marketing strategies that all hospitals and clinics require, which is a responsibility that could readily be assigned to interested clinical faculty members of the CPH Department. The hospitals could also contract with the department to develop or modify their clinical information systems, and establish health risk assessment programs and health technology evaluations, that would benefit the hospital and medical school, all without inflated payments to commercial companies.

CPH Departments could also utilize their Health Statistics Centers to develop disease registries modeled after our Maryland Cancer Registry (MCR). These would perform the functions of the MCR on a regular basis, but also become government-sponsored centers for collecting regional data on trends in mortality and incidence of other pandemic agents, which would have far more credibility than the COVID-19 statistics that confused the public and cost a fortune to generate. In doing so, the CPH Departments would become more relevant to the other departments of the medical or public health school, while generating funds to support the CPH and its Health Statistics Center (Chapter 12).

WHERE SHOULD THE NEW PROGRAM BEGIN?

Over the past several decades, the leadership of public health and medical school departments has gradually moved from

clinically trained physicians with strong interests in disease pathogenesis and healthcare management to individuals, often lacking clinical backgrounds, who are primarily concerned with contemporary issues involving diversity, climate change, and a host of other societal, rather than specific health, issues. The consequences of this dramatic change led to the abolition of bioscience entrance requirements and a laissez-faire curriculum seemingly designed for students without healthcare or clinical career interests. Most of such students are excited about their careers in ancillary health realms, which offer decent salaries and travel to exotic sites of disease, but few graduate with the skills to assume critical roles in healthcare, biomedical research, or educating the next generation of public health practitioners.

The ultimate result of the developments described above should be apparent to anyone concerned with the nation's leadership in healthcare which, in the past, was the product of a high quality of biomedical education, research, and public health practice in our medical and public health schools. The elimination of bioscience admission requirements opened the floodgates to thousands of applicants who would never have been accepted to such graduate programs previously, and resulted in curriculum revisions largely devoid of bioscience and clinical medicine. The matriculation of this new class of students was a bonanza for the schools' fiscal officers, but a pyrrhic victory otherwise, as the clinically educated students quickly lost interest in the programs, while the research projects of most doctoral students abandoned biomedical and clinical subjects in favor of hypothesis-free social agenda projects of interest to their schools and mentors.

The effort to revise public health education should probably not begin in a public health school. These are now large

academic entities, with thousands of students, highly diverse faculties, unique relationships with their own universities, and sizeable endowments. My suggestion would be to start the revival process by establishing CPH Departments at a small number of well-regarded medical schools, which already have Public Health Departments with diverse faculties, sizeable student bodies, a respectable research output, and a favorable reputation. The department at the University of Maryland, which I chaired several decades ago, would have made an excellent choice but, unfortunately, the university administration has now developed a public health school in College Park, an hour away from the medical school, and is unlikely to be interested.

Many of today's Public Health Departments are much smaller and less ambitious than ours was at the University of Maryland. For such departments, teaching large numbers of medically uneducated students about societal concerns in healthcare is now a dominant activity, and their research is often in the form of collaborative studies designed and managed by national committees, with little input by individuals, faculty, or students. Few members of these faculties are seriously devoted to epidemiology-centered education and classical public health investigations. They are not among the leaders of research in disease pathogenesis or prevention, nor do they address serious clinical care issues like we did in our studies on artificial sweeteners in bladder cancer, or are they equipped to develop bona fide cancer registries, or the design of health risk assessment instruments for medical practice.

After the initial CPH Departments have recruited their basic faculties, begun teaching clinically oriented epidemiological courses, and undertaken relevant projects like those described

in this volume, more intense relationships will develop between the medical school's clinical departments and their newly reconstituted public health neighbor, the CPH Department. Instead of struggling to educate clinically unschooled students with little interest in issues of clinical relevance to patients with disease, the newly established CPH Departments will emerge over time as the leading practitioners of epidemiologic research, while they earn fee-based revenues from a growing list of ventures for the hospital, the medical school, and government health agencies.

Strengthening the clinical content of the public health curriculum could be rather quickly realized at a few carefully selected medical and/or public health schools. An early consequence would be the growing popularity of public health careers among newly matriculating physicians and nurses. The clinically competent CPH Departments could schedule seminars devoted to the clinical discoveries of their own faculty and student researchers. This will strengthen relationships with the other medical school departments, which will be invited to utilize the epidemiological and biostatistical resources of the CPH Department for their own research purposes. Eventually, students in clinical and basic science departments would be induced to enroll in relevant epidemiological and biostatistical courses offered by the CPH Department.

During my tenure at the University of Maryland, its Public Health Department was ideally configured for the activities described in this volume, as well as for the modifications we are recommending. During most of my tenure, the dean and president of the university permitted our initiatives to be implemented, though funds were usually expected to be garnered by the department rather than the medical school. The faculty grew substantially in clinically trained

epidemiologists, biostatisticians, computer technologists, and an array of assistants, interviewers, nurses, and miscellaneous study staff during this period. We continued to mount classical epidemiological studies and, with the arrival of the computer age, undertook an increasing number of computer-based initiatives, including some that competed with commercial organizations.

The departmental organization developed at the University of Maryland could serve as one model for meeting the future needs of CPH Departments in other university settings. It was the home base for all the educational and research programs described in this volume, and it succeeded in this effort at much lower cost than one would expect. If the fee-for-service income anticipated for the CPH Departments could be managed in the same fashion as the clinical income of the clinical departments, a new era in medicine and public health will have arrived. The CPH Departments will have attained parity with the clinical departments in contributing financially, scientifically, and educationally to the medical school, their public recognition would grow, and the long-term security of CPH would be assured.

LONG-TERM IMPACT OF THE CPH DEVELOPMENT

The recommendations offered in this volume will clearly benefit the epidemiological divisions of both medical and public health schools. They would lead to a revival and reinvigoration of departmental programs that have persisted for years in the academic doldrums. The deans at these schools should be attracted by the depth and variety of the innovative educational and research opportunities to be offered matriculating physicians and nurses, as well as the fee-for-service income pathways built into the system.

Newly enrolled medical and nursing students will quickly sense the camaraderie of an environment in which everyone, trainees and faculty alike, share an abiding interest and a substantial background in clinical medicine and public health. Rather than interacting with classmates who are just beginning to explore careers in vaguely defined aspects of health, they will relate to colleagues who are fully committed to lifetime service in human health and disease. These relationships will greatly enrich the learning environment, and go far beyond casual repartee with students who will probably choose to work in federal, state, or commercial health agencies, rather than teaching, investigating human disease, and contributing to the long-term survival of public health.

ENVOI

This book calls for a multiplicity of actions aimed at establishing Clinical Public Health Departments and associated Health Statistics Centers in a number of medical and public health schools in the United States and abroad. After the legal requirements have been fulfilled, a major effort must commence to attract the epidemiological faculty and the clinically experienced physicians and nurses who will enroll as students. Simultaneously, the curriculum must be upgraded, and a host of new ventures to reinvigorate public health and yield revenues never before sought by public health institutions would be initiated. The epidemiological leadership for all these endeavors must collaborate to assure that their mutual biomedical efforts satisfy the Latin principle of In Specialibus Generalia Quaerimus ["We seek the general in the specifics"], a basic precept of epidemiology (Lankester,1902, 394-396).

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SUBJECT INDEX