

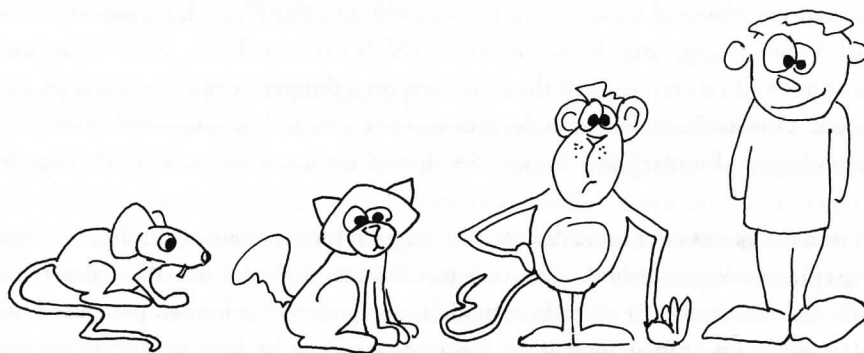
INTRODUCTION TO Public Health

Third Edition



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The Biomedical Basis of Chronic Diseases



Evolution of the Research Study

The early successes of public health against infectious diseases led to a change in the major causes of illness and death beginning in the 1920s. Chronic degenerative diseases, especially heart disease and cancer, are now the leading causes of death in the United States. While they are primarily diseases of old age—when everyone must die of something—they also strike people in their prime, robbing them of productive years of life. Cancer is the leading cause of death among Americans aged 45 to 65, and cardiovascular disease runs a close second. Cardiovascular disease kills the most people overall. Other significant diseases of current public health concern include diabetes, arthritis, and Alzheimer's disease, which may not be as deadly in the short run but have severe impacts on the quality of life. It is the mission of public health to prevent such premature death and disability.

Prevention of disease usually requires some understanding of the cause, a requirement that is generally much more difficult to fulfill for chronic diseases than for infectious ones. There is no single pathogen that causes cancer or heart disease, nor is there one for arthritis, diabetes, or Alzheimer's disease. In most cases, chronic diseases have multiple causes, making it more difficult for scientists to recognize significant risk factors and establish preventive measures.

Moreover, these diseases tend to develop over long periods of time, further complicating the task of pinning down causes. In some cases, however, the gradual onset provides the advantage of early detection, permitting secondary prevention—interventions early in the disease process that can mitigate its impact.

As chronic degenerative diseases became a growing problem during the 20th century, scientists began to focus on efforts to understand their causes. The growth of the National Institutes of Health (NIH), which sponsors most biomedical research in the United States, has reflected the growth of concern about these diseases. In its early days as a one-room Laboratory of Hygiene that opened in 1887, the NIH conducted research primarily on infectious diseases. Congress created the National Cancer Institute in 1937 and the Heart Institute—now called the National Heart, Lung, and Blood Institute (NHLBI)—in 1948. Now there are 27 different institutes and centers, each of them focused on a different organ or problem, mostly chronic diseases. One institute, for example, is concerned with arthritis, one with diabetes, and one with neurological disorders and stroke. (See list of institutes and centers in Chapter 3, Box 3-2.)

Research into the causes of chronic disease, like research into the causes of infectious disease, relies on the epidemiologic methods discussed in Chapters 4–6 and on laboratory research, which usually includes studies of animals as models, or stand-ins for human patients. The importance of research on animal models to the understanding of human disease cannot be overemphasized. Epidemiology is generally limited to observation and analysis of events that occur spontaneously. Ethical concerns severely limit the experiments that can be done on humans. In experiments on laboratory animals, scientists can carefully control the conditions so that cause-and-effect relationships can be clearly proven. Mice and rats are the most commonly used laboratory animals; as mammals, they share the majority of biochemical and physiological processes with humans. Because of their short life spans, the effects of various exposures and interventions can be studied over the lifetime of the animals. However, mammals can differ in unpredictable ways in their susceptibility to infectious or toxic agents. Different experimental animals have proven useful for studying different diseases, and extrapolation of results from any particular mammal to humans is not always valid.

The identification of an animal model can significantly improve progress toward understanding a disease. It is not always easy to find an experimental animal that is susceptible to the disease one wishes to study. For instance, there is no good animal model for AIDS, a fact that has hampered progress in developing drug therapies or vaccines. Asian macaque monkeys, which can be made sick by simian immunodeficiency virus, a relative of human immunodeficiency virus (HIV), are the closest substitute. Only chimpanzees can be infected with HIV, and chimps are no longer used for research for ethical reasons and cost.¹ Animals also differ in how

they metabolize some chemicals; a dose of dioxin that would kill a guinea pig has no effect on a mouse or rat, and it is difficult from this evidence to predict the chemical's toxicity to humans.

Scientists have been increasingly successful in devising methods of growing cells and tissues in laboratory glassware for studying biomedical processes. Such laboratory cultures are commonly used to investigate the cancer-causing potential of various chemicals. Much of the research on HIV has been done using cultured human cells, and a great deal has been learned. However, such experiments provide oversimplified conditions that may lead to invalid conclusions about the complex interactions that occur in intact animals. In the case of HIV, for example, a number of drugs that appeared to inactivate the virus in test tube experiments have proved to be ineffective in human patients.

Cardiovascular Disease

Cardiovascular disease encompasses two of the three leading causes of death in the United States: heart disease and stroke. Risk for dying from cardiovascular disease increases with age, is higher in men than in women, and is higher in African Americans than in whites.

The causes of cardiovascular disease have been relatively well established through epidemiologic studies, including the Framingham Study described in Chapter 4, which identified high blood cholesterol, high blood pressure, and smoking as major risk factors. Animal experiments and examination of the bodies of people who have died of the disease have also contributed to an understanding of how it develops. Knowledge about cardiovascular disease has been facilitated by its prevalence in the United States and the fact that it follows a similar progression in many of its victims. The important role of blood components in determining individual risk was readily established because blood is easy to study; it can be drawn from patients and experimental subjects without major discomfort or ethical objections.

It has been known for decades that atherosclerosis—hardening of the arteries—is part of the development of cardiovascular disease. Pathologists performing autopsies on people who died of heart attacks found, within the inner-wall lining of the deceased's arteries, a buildup of plaque composed of fat and cholesterol, blood cells, and clotting materials. The formation of plaque begins at an early age in the United States. Fatty streaks, the first stage in the development of plaque, have been found on autopsy in half the children aged 10 to 14 who died of accidental causes.² A classic study, published in 1955, examined the arteries of American soldiers killed in the Korean War and found that 77 percent of the men, whose average age was 22, showed some signs of atherosclerosis.³ More recent studies have confirmed these findings and have shown that plaque was more likely to be found in adolescents and young adults with risk factors such as smoking, hypertension, obesity, and high levels of low-density lipoprotein cholesterol.⁴

Animal studies showed that diet plays a role in the formation of plaque. Rabbits fed milk, meat, and eggs instead of their normal vegetarian diet were found to develop atherosclerotic plaque very similar to that found in humans.⁵ It was easy to deduce that the American diet was responsible for the high rate of cardiovascular disease in the United States.

Experiments on rats, rabbits, and monkeys have clarified the process by which high cholesterol and fat in the blood interact with other risk factors such as smoking, high blood pressure, and diabetes to form plaque in the arteries. These factors cause chronic injury of the artery's inner wall, which the body attempts to repair, leading to a "healing" process that runs wild, becoming a disease in itself. The higher the levels of cholesterol and other fats in the blood, the more they are incorporated into the scab-like buildup, and the faster the plaque forms. A heart attack or stroke results when the plaque ruptures, releasing clots that may block an artery in the heart or brain, cutting off the blood supply.⁶

Recent evidence suggests that atherosclerosis may also have an infectious component caused by bacteria that are often found in plaque.⁷ The blood cells in plaque are characteristic of an immune response, and a number of chemicals in the blood suggest that atherosclerosis is an inflammatory condition like arthritis. These findings may lead to new approaches to prevention, diagnosis, and treatment of atherosclerosis.⁶

With the major risk factors for cardiovascular disease well established, much of the recent epidemiologic and biomedical research has focused on trying to understand what determines the relative presence or absence of these risk factors. A great deal has been learned about the various lipids (fats) in the blood, each of which plays a role in the individual's risk of cardiovascular disease, and how their concentrations may be increased or decreased. Factors that affect blood pressure have also been extensively studied. Diabetes, which has its own research institute at NIH, greatly increases the risk of cardiovascular disease (see later in the chapter for a discussion of the biomedical basis of diabetes). All of these risk factors are determined in part by genetics, but they can be significantly modified by individual behavior and are thus susceptible to public health intervention.

High blood cholesterol is a well-known risk factor for atherosclerosis and heart disease. Cholesterol levels of 200 mg/dL (milligrams per deciliter of blood) or below are considered desirable: persons with that level of cholesterol have less than one-half the heart attack risk of those with levels above 240 mg/dL.⁸ Most of the cholesterol in the blood is bound up with protein in various forms, and some forms are more harmful than others. For example, if a high percentage of a person's cholesterol is in the form of high-density lipoprotein (HDL), sometimes called "good cholesterol," the person's risk of heart disease is much lower than that of someone with a high percentage of cholesterol in the form of low-density lipoprotein (LDL), "bad cholesterol." Many current studies try to identify factors that affect not only total cholesterol, but also the relative concentrations of HDL and LDL.

The main sources of cholesterol in the American diet are eggs, meat, and milk. In humans, as in rabbits, vegetarians have lower cholesterol levels than meat eaters. Vigorous exercise lowers total cholesterol and increases HDL. Moderate consumption of alcoholic beverages has a similar effect, although heavy drinking damages the heart. Other dietary substances such as fish, olive oil, and oat bran also appear to have favorable effects on blood lipids. Smoking lowers HDL levels. Genes play an important role in the HDL-LDL balance. Some people can eat lots of fat with very little effect on their blood cholesterol, while others must work much harder to maintain favorable levels.

In the past decade, the use of cholesterol-lowering drugs called statins has increased dramatically. The number of Americans who took the drugs grew from about 2 million in 1998 to 30 million in 2005.^{9,10} Epidemiologic studies have clearly shown that statins can prevent heart attacks, even in people with cholesterol levels previously considered normal and, for the most part, they appear to be safe for long-term use. However, from a public health perspective, the trend toward prescribing drugs for healthy people to take for the rest of their lives is troubling. Moreover, statins can be expensive. As a spokesman for the American Heart Association is quoted as saying, "If you're going to increase my health insurance because my next door neighbor has borderline high cholesterol, and if he's sitting around and watching TV and eating and getting fat, do you want me to pay for that?"¹¹

While the availability of statins appears to be good news for secondary prevention in people who already have atherosclerosis or who have risk factors that put them at high risk, the preferable public health approach to preventing heart disease is primary prevention. This means promoting healthy behavior, including exercise, not smoking, and eating a healthy diet. Eating a healthy diet is not easy in American society. Chapters 16 and 23 discuss the role of public health in promoting good nutrition. Other aspects of social and behavioral factors in health are also discussed in Part IV.

High blood pressure—hypertension—is a major risk factor for cardiovascular disease, especially stroke, contributing to the injury in the artery walls that is part of atherosclerosis. It also increases the risk of kidney disease. While some medical conditions are known to cause high blood pressure, most cases occur without known cause, and these people are said to have "essential hypertension." Factors that have been linked with essential hypertension are obesity, smoking, lack of exercise, and stress. In the United States, 140/90 is generally considered the borderline above which blood pressure is considered too high. In this reading, 140 is the systolic pressure, that pressure exerted by the blood on the artery walls during the heart's contraction when the pressure is greatest. The diastolic pressure—90 in this case—occurs between contractions, when the heart is relaxed. New evidence prompted the NHLBI to issue guidelines in 2003 that classified blood pressure as "normal" only if it is below 120/80. Pressures between

this level and 140/90 are classified as "prehypertension," meaning that individuals with these readings are at risk of developing hypertension. Since the risk of stroke rises continuously as blood pressure rises, people are advised to take medication if necessary to maintain a healthy blood pressure. For those with other risk factors, such as diabetes or kidney disease, it is even more important to keep blood pressure under control.¹²

The U.S. government launched a major blood pressure awareness program in 1972; since then, the annual rate of fatal strokes has been cut by more than half. Many people can keep their blood pressure under control by eating a healthy diet, exercising, and abstaining from smoking, the same behaviors that promotes healthy cholesterol levels. Secondary prevention is important: people should know their own blood pressure and take appropriate measures if it is too high.

Dietary salt (sodium chloride) is believed to be a factor in causing some cases of essential hypertension, but sensitivity to salt is variable and is probably determined by genetics. Laboratory studies have found that some strains of rats get high blood pressure when fed large amounts of salt, while rats of other strains do not seem to react to salt. Rats of one sensitive strain tend to have strokes when subjected to salt and stress, while rats of some other strains are unaffected.¹³ The NHLBI recommends that everyone limit their salt intake to about a teaspoon a day, but the question of whether this measure would reduce blood pressure in the average person is controversial. Some researchers have argued that high dietary salt damages the heart and kidneys even in people with normal blood pressure.¹⁴

At a population level, it is clear that hypertension has a higher prevalence in groups that consume greater amounts of sodium, and that sodium intake is higher in the United States than in many other countries. The prevalence of hypertension in the United States is high; one in three adults have high blood pressure; over half of those age 60 or older have it.¹⁵ Therefore public health experts have noted that reducing the amount of salt in the American diet would be expected to reduce the prevalence of hypertension. They estimate that, for example, if the average systolic blood pressure could be reduced by five points, mortality due to stroke would be reduced by 14 percent. Because Americans tend to get most of their salt from packaged foods and restaurant meals, the American Public Health Association together with an interagency committee coordinated by NHLBI, has recommended that the food industry, including manufacturers and restaurants, reduce sodium in the food supply by 50 percent over the next decade.¹²

Smoking is believed to increase the risk of cardiovascular disease through the actions of two components of tobacco smoke: nicotine and carbon monoxide. Nicotine, the addictive component of tobacco (as discussed in Chapter 15), is a stimulant that raises blood pressure, increases the pulse rate, stimulates release of stress hormones, and increases irritability of the heart and blood vessels. Carbon monoxide, a poisonous gas, binds to hemoglobin in the blood, blocking

the hemoglobin's ability to carry oxygen throughout the body. Both nicotine and carbon monoxide place stress on the heart and blood vessels, with the long-term effect of contributing to atherosclerosis. In the short term, the effects of nicotine and carbon monoxide can provoke irregularities in heartbeat, which may result in sudden death.

Tobacco is especially significant as a cause of heart attack in younger adults. While heart attacks are relatively rare among people in their 30s and 40s, those that do occur are likely to be caused by smoking. One epidemiologic study found that smokers in this age group have a five times greater rate of heart attacks than nonsmokers.¹⁶

Cancer

Cancer has proven much more difficult to understand than cardiovascular disease, in part because it has so many different manifestations. It is sometimes said that cancer is not one disease, but 100 diseases. In many ways, breast cancer is different from lung cancer, which is different from leukemia. They typically differ in terms of risk factors, appearance under a microscope, response to various forms of treatment, and so forth. For the biomedical scientist and the public health professional trying to understand cancer cause and prevention, each kind of cancer must be studied separately. What all cancers have in common is that they arise when the activities of a cell are transformed and the cell begins to grow out of control. Understanding cancer, therefore, requires understanding normal cell function, so that it is possible to recognize what goes wrong in a cancer cell. In general, a normal cell turns cancerous through a mutation in the genetic material, DNA—usually a mutation in one of the genes that regulate cell growth and differentiation. When that cell divides, the mutation is transmitted to the daughter cells, which, because of the disruption in control caused by the mutation, tend to divide more rapidly than normal. As the cells continue to divide abnormally, errors tend to occur as the DNA is copied, leading to additional mutations and more abnormalities in the cells that are becoming a tumor.^{17,18} Other changes that may accompany the formation of a tumor are the stimulation of the growth of blood vessels that feed the tumor and the tendency to metastasize—a process by which cancer cells detach from the main tumor and spread to distant parts of the body. Understanding the molecular mechanisms through which tumors form and grow can lead to the development of effective therapies, specific approaches to halting the process or killing the cancerous cells.

To achieve the public health goal of preventing disease, it is important to know what causes the mutations that initiate the cancer. It turns out that mutations in DNA can be caused by many different types of agents, including chemicals, viruses, and radiation. Other factors, such as hormones and diet, play a role in determining whether a mutation progresses to the develop-

ment of a tumor. Hormones, which function in the body to stimulate or inhibit cell growth, may have an enhanced effect on a mutated cell. The mechanisms by which dietary factors influence the development of cancer—in addition to the fact that some foods may contain carcinogens, or cancer-causing chemicals—are less well understood. There is some evidence that dietary fiber protects against some cancers, perhaps because it speeds the passage of possible carcinogens through the digestive tract, lessening the likelihood that they will be absorbed. High fat in the diet increases the risk of many forms of cancer, but it is not clear why. Diets high in fruits and vegetables seem to be protective.

Exposure to certain kinds of radiation has long been known to cause cancer in humans. Many of the early scientists who unsuspectingly worked with radioactive materials died of the disease, including Marie Curie, the Nobel Prize winner who discovered radium. Curie died of leukemia in 1934 at age 66.¹⁹ Laboratory studies demonstrated clearly that ionizing radiation was capable of damaging DNA and causing mutations in all forms of life, from bacteria to plants to mammals. Later, exposure to certain chemicals was observed to cause some of the same kinds of genetic damage as did radiation, and many of these same chemicals could be demonstrated to cause cancer in laboratory animals.

Viruses have long been known to cause some cancers in plants and animals, but only recently have some human cancers, including liver cancer and cervical cancer, been shown to be of viral origin. Cancer viruses transform cells by integrating themselves into the DNA of the host cell; the viral genes may override the host's genes, for example, by turning on inappropriate cell division. In fact, viruses that cause cancer in humans have been found to carry altered forms of human genes.

The knowledge gained by studying cancer viruses has helped scientists to understand more generally how mutation of the cell's own genes can turn a normal cell into a cancer cell by inappropriately turning on cell division. Some of the genes that, when mutated, lead to cancer—known as oncogenes—stimulate cell division; others, known as tumor suppressor genes, normally function to keep cell division turned off. The new genetic understanding of cancer causation also helps to explain why some families are more susceptible to some kinds of cancer. Since in most cases more than a single mutation is required before a cell is fully malignant, a member of a family that carries one mutation in a gene might need only one additional event to develop a tumor.

The public health approach to primary prevention of cancer is to prevent human exposure to the agents that cause mutation. In the case of ionizing radiation, the danger of which was recognized early, government standards have been developed to protect the population against exposure from various sources such as nuclear power plants, medical and dental x-rays, and radon gas. Sunlight, another proven cause of cancer, cannot be regulated: education in the importance of sunscreen and hats is the favored approach. Because viruses have only recently been

recognized to cause cancer in humans, the public health response to these agents is evolving. Immunization is one approach: Hepatitis B vaccination is now recommended for all children, not only to prevent acute hepatitis infection but because chronic infection with hepatitis B virus has been shown to lead to liver cancer. A recently developed vaccine against human papilloma virus has been shown to be effective for the prevention of cervical cancer. It is controversial, however, because it must be given to young girls before they become sexually active.

The extent to which chemicals in the environment cause cancer is one of the most difficult and controversial questions in public health. The tars in tobacco smoke are clearly a major cause, and the American Cancer Society estimates that almost one-third of cancer deaths in the United States are due to tobacco use.²⁰ In addition to being the major cause of lung cancer, smoking increases the risk of cancer in many other organs, including the mouth, nasal cavities, larynx, pharynx, esophagus, stomach, liver, pancreas, kidney, bladder, and cervix. Although Americans are greatly concerned about the possibility of cancer-causing chemicals in their food, water, or air, little is known about whether these sources contribute significantly to the number of cases diagnosed each year. Most industrial chemicals have not been tested for carcinogenicity. Chemicals added to food, however, must be tested. Regulations on food additives are discussed in Chapter 23.

The testing of chemicals for carcinogenicity in humans is fraught with difficulties. The standard, most definitive approach is a controlled experiment in which a large group of rats, mice, or guinea pigs is fed a diet containing the suspect chemical over their whole lifetime—about two years for these animals—and the incidence of tumors in this group is compared with that in an equivalent group of animals that did not receive the chemical. If the exposed animals have more tumors than the unexposed, the chemical is labeled a carcinogen. Aside from the potential frustration of the experiment by some unpredictable factor—for example, an epidemic of mouse flu that kills off all the animals after the first year, necessitating a new start—there are many reasons why this approach may not accurately predict carcinogenicity in humans. Differences in metabolism between mouse and human sometimes mean differences in carcinogenicity of a chemical in the two species; or the dose of the chemical necessary to produce a detectable increase in tumors may be so high that it disrupts the animals' metabolism, making the results meaningless.

Another approach to determining carcinogenicity—one that is much faster, simpler, and cheaper—is to test whether the chemical can cause mutations in a colony of cells growing in a laboratory dish. This test has its own drawbacks. While mutation is necessary for the development of cancer, not all chemicals that cause mutations are carcinogens. These test-tube experiments ignore the role of hormones and other secondary influences that determine whether a mutated cell will actually grow into a tumor.

Part V discusses further the importance of environmental factors in causing cancer.

Diabetes

The number of Americans diagnosed with diabetes is rising rapidly, having more than tripled in the past twenty years.²¹ Officially, diabetes ranks sixth overall as a cause of death in the United States; it is fifth among blacks, Hispanics, and Asians, and fourth among American Indians.²² However, there are reasons to believe that diabetes contributes to premature death more often than reported by death certificates. Examination of death certificates of people known to have diabetes have found that only 35 percent to 40 percent of them had diabetes listed anywhere on the certificate. Many deaths listed as caused by heart disease may be linked with diabetes. Heart disease death rates are two to four times higher for people with diabetes than for those without it. Overall, the risk of death for people with diabetes is double the risk for people of the same age who do not have diabetes.²³

Diabetes is a major cause of disability. Although it is usually treatable and can be controlled over long periods of time, there has been little that public health could do to prevent the disease except to make unpopular recommendations for changes in lifestyle. The Centers for Disease Control and Prevention (CDC) refers to twin epidemics of diabetes and obesity,²⁴ because obesity greatly increases the risk of diabetes, and the number of Americans who are obese has been increasing rapidly, as discussed in Chapter 16.

Diabetes is a deficiency in the body's ability to metabolize sugar, a function that is normally controlled by the hormone insulin. There are two major forms of diabetes: type 1 diabetes, which usually has its onset in childhood, is caused by a failure of the insulin-producing cells of the pancreas; type 2 diabetes, more common with increasing age, is a more complex mix of impaired insulin production and resistance to the hormone's action. Both forms of diabetes are significantly affected by genetics. Research on the causes of diabetes has thus far yielded very little information on how type 1 diabetes could be prevented. Type 2 is closely correlated with obesity, and is largely preventable with proper diet and exercise. However, public health has not been very successful in persuading most people to adopt such healthy behaviors, which could prevent a number of other chronic diseases as well, as discussed in Chapter 16.

While public health may not be able to prevent diabetes, it is concerned with preventing the disability that is inevitable when the disease is not well controlled. An estimated one out of four people with diabetes are unaware that they have it.²⁵ This is a major public health problem because the high blood sugar that is typical of uncontrolled diabetes causes damage to blood vessels throughout the body, especially the eyes and kidneys. Complications of diabetes include blindness, kidney failure, cardiovascular disease, poor wound healing, and amputations of the extremities. Secondary prevention requires early diagnosis of the disease so that treatment can begin at an early stage. Lack of access to routine medical care—a common problem in the

United States—contributes to the seriousness of diabetes as a public health problem. The necessary long-term monitoring and treatment required to manage a case of diabetes can be complicated and expensive, and those who need it the most may have the greatest difficulty in receiving care, as discussed in Chapters 25 and 26.

Other Chronic Diseases

There is much more to learn about other diseases that have a major impact on the health of the population. Mental illness is a major cause of disability in this country, and yet very little is known about its causes and prevention. Alzheimer's disease and other forms of dementia in older people, discussed in Chapter 28, cause anguish to their families and force affected people into nursing homes at a tremendous cost to society. The NIH and other funding sources are supporting a great deal of research on understanding genetic and other factors that affect people's risk of developing dementia as they age, but not much is known yet on how people can protect themselves. Arthritis, while not a major killer, can severely impact the quality of life for many older people, causing great pain and suffering in their last years.

Conclusion

Chronic diseases are the leading causes of death and disability in the United States, with cardiovascular diseases and cancer leading the list. Diabetes is becoming increasingly prevalent and is a major cause of disability. Preventing these diseases—an important public health priority—is based on understanding their causes. The success of biomedical science and epidemiology in understanding causes of cardiovascular disease and how to prevent or delay its onset serves as a model for what society would hope to achieve for all the diseases that cause premature death or disability. Progress in understanding the functioning of normal cells and what goes wrong when they turn malignant gives researchers hope that they will eventually learn to prevent many kinds of cancer.

Despite the tremendous progress made by biomedical science in the understanding of the bases of chronic diseases, a great deal is left to learn about what can go wrong with the human body and how to prevent it. People cannot expect, and maybe would not wish, to live forever, but biomedical research holds the key to preventing many premature deaths, as well as much of the pain and anguish that many people suffer toward the end of their lives. Because it offers such hope, NIH's work is generally well supported by Congress and the American people.

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