Heart disease has been identified—correctly—as the number one killer in the United States. Despite this fact, government funding of research into the causes and treatment of diseases of the heart and blood vessels has lagged significantly behind that of cancer research. Passage by Congress of the Heart, Lung, and Blood Act of 1972 did improve the situation, however. The budget of the National Heart, Lung, and Blood Institute has increased from $233 million for fiscal year (FY) 1972 to $397 million for FY 1977. In addition, the American Heart Association will spend almost 20 million dollars for research in the coming year.

The question then might be, What does this money buy? During the next few weeks, a series of articles will examine some of the recent developments in research on cardiovascular diseases. Not intended to be exhaustive, the articles will focus on progress in understanding the biological mechanisms underlying the diseases. This research is providing the kind of information needed to prevent or cure a disease—not just control its symptoms. Clinical advances in treating hypertension and abnormal heart rhythms, in limiting the damage to heart muscle caused by heart attacks, and in detecting and measuring the extent of heart disease will also be considered. Although money spent for research has not yet brought about the removal of cardiovascular disease from its position as the leading cause of death, the research is laying the foundation that may one day permit the attainment of that goal.

Epidemiology of Heart Disease: Searches for Causes

Cardiovascular diseases—diseases of the heart and blood vessels—are the leading cause of death in this country. They afflict more than 28 million people and are responsible for about 1 million deaths per year in the United States alone. This means that half of all deaths in this country can be attributed to cardiovascular diseases. Although the incidence of the diseases increases with age, they are not limited to the elderly. For example, one-fourth of all heart attack deaths occur before the age of 65.

Needless to say, medical scientists would like very much to know what causes cardiovascular disease in the hope that this knowledge would permit prevention of the diseases and a large reduction in the death rate. The causes, if any simple ones exist, have eluded investigators despite the expenditures of large amounts of time and money. However, several factors that appear to contribute to the development of cardiovascular disease have been identified. The evidence comes from the results of three types of research: epidemiological, biochemical, and clinical. This article will concentrate on the epidemiological studies; future articles will discuss some of the biochemical and clinical evidence concerning the etiology of heart disease.

Epidemiology often parallels the other types of research by providing indications of what conditions are associated with or predispose people to develop cardiovascular diseases. Other methods can then be used to investigate the mechanisms by which the conditions cause the diseases and whether modifying the conditions can prevent the diseases.

Since World War II, epidemiologists have studied populations all over the world to see whether the incidence of cardiovascular diseases varies among different populations. They found that the incidence does vary and is related to several risk factors, particularly cigarette smoking, high blood pressure, and high concentrations of serum cholesterol.

Observations of long-term trends in mortality in general and in mortality due to cardiovascular diseases in particular may also shed light on the possible causes of these diseases. Such observations have recently revealed an encouraging fact: the death rate from cardiovascular diseases in the United States has declined markedly during the past several years.

In 1975, according to investigators at the National Center for Health Statistics, 979,180 people died of the major cardiovascular diseases. This is the first time since 1967 that the number of such deaths was less than 1 million. The conditions included as major cardiovascular diseases (see box) by the center are hypertension and hypertensive heart disease; coronary heart disease, including heart attacks and angina pectoris; stroke; chronic diseases of the heart muscle or membranes; heart failure and shock; and arteriosclerosis. Congenital heart defects and diseases of the veins, such as phlebitis, were not included.

The death rates, calculated for each age group or adjusted to compensate for the changing age distribution of the population, for all the categories of major cardiovascular disease have been dropping since 1968. Cardiologists are especially gratified by the decrease in the death rate from coronary heart disease, which killed approximately 680,000 people in 1975 and which is the biggest contributer to the overall cardiovascular death rate. Between 1970 and 1975, the decrease was 13 percent, a savings of about 15,000 lives per year. This is an apparent reversal of a trend that began before 1940. Between 1940 and 1960 the mortality rate from coronary heart disease increased steadily. It plateaued between 1960 and 1967 and then began decreasing.

Epidemiologists would like to see the trend continue for a few more years in order to be sure it is not a statistical quirk. Most believe the trend is real but no one has a sure explanation for it.

Since high blood pressure, cigarette smoking, and high concentrations of serum cholesterol are thought to predispose people to develop heart disease, investigators are asking whether decreases in the frequency of these traits in the U.S. population may have contributed to the decrease in mortalities from these diseases. So far, the evidence is suggestive but inconclusive.

Hypertension can be treated with drugs, and there is evidence that adequate control of this condition can decrease the risk of developing cardiovascular diseases. The death rate from hypertension itself dropped 28 percent from 1970 to 1975. But the contribution of drug treatment to the decrease in mortality cannot be evaluated yet. One anomaly is that the downward trend in the rates began before the drugs became widely available, according to Tavia Gordon and Thomas Thom of the Biometrics Research Branch of the National Heart, Lung, and Blood Institute (NHLBI).

Nevertheless, recent data compiled by the National High Blood Pressure Education Program of the NHLBI indicate that between 1971 and 1974 there was a significant increase in the percentage of cases of hypertension that were diagnosed. Moreover, it appears that a higher percentage of persons who are aware of their high blood pressure have their condition under control than before 1971. One problem with this analysis is that the population surveyed in 1974 may not be comparable to those surveyed previously. Nonetheless, many investigators think that better control of hypertension may be contributing to the downward trend in cardiovascular mortality.

Results of studies performed by the

American Cancer Society (ACS) indicate that the recent decreases in cigarette smoking and the shift to low-tar, low-nicotine cigarettes may have contributed to the decline in mortality from cardiovascular diseases. Persons taking part in these studies who smoked cigarettes low in tar and nicotine had lower death rates from both lung cancer and coronary heart disease than participants who smoked comparable numbers of high-tar, high-nicotine cigarettes. Nonsmokers, however, still fared much better than smokers of even the low-tar cigarettes. Robert Levy, director of the NHLBI, points out that the carbon monoxide present in cigarette smoke may contribute to the development of heart attacks but not of lung cancer so that a cigarette "safe" for the lung may not necessarily be "safe" for the heart.

Despite the results of the ACS studies, the effects of changing smoking habits on the mortality rates for cardiovascular diseases are not yet determined. For example, more men than women have stopped smoking, but Gordon and Thom say that both sexes have experienced equal decreases in mortality from these diseases. Sorting out the effects of cigarette smoking from those of other risk factors whose prevalence differs between the two sexes will not be easy.

The role of changes in diet is especially complex. Jeremiah Stamler of Northwestern University Medical School says that people in this country have decreased their consumption of some foods with high cholesterol and saturated fat content (including eggs, whole milk, and butter) but have increased their consumption of others, beef in particular. Consequently, it is difficult to assess the net effect of these changes on the cholesterol and fat content of diets, and whether the changes have affected mortality from heart disease.

Besides looking for evidence that Americans may have changed their living habits, investigators have asked whether other factors may have affected mortality rates from cardiovascular diseases. One possibility, which improves the likelihood that people who suffer heart attacks will survive, is better medical care. This effect would be magnified by the widespread availability of coronary care units, specially trained ambulance crews, pacemakers to regulate the heart beat, and cardiopulmonary resuscitation techniques. But Stamler points out that the impact of coronary care units is necessarily limited by the fact that 70 percent of those who die from heart attacks die before they reach the hospital.

During the last few years, there has been a dramatic increase in the number of coronary bypass operations. Richard Ross of the Johns Hopkins University Medical School estimates that about 65,000 patients per year now undergo this procedure, in which diseased and blocked coronary arteries are replaced with healthy blood vessels taken from another part of the body. Although cardiologists agree that the operation can relieve the symptoms of severe, intractable coronary heart disease, no one knows whether it improves long-term survival rates. Stamler says that it is not now possible to determine whether the operation has had any impact on heart disease mortality rates.

Gordon and Thom suggest that the trend in coronary heart disease mortality rates may not result from voluntary actions of the American people. They point out that there has been a general decrease in the death rates in virtually all categories with a few exceptions such as cancer, accidents, and violence. Respiratory infections, such as influenza and pneumonia, often contribute to the deaths of people weakened by other diseases, including those of the circulatory system. Because the influenza epidemics since 1968 have killed comparatively few people, Gordon and Thom think that the decrease in the death rate from coronary disease may result in part from the freedom from the stress of influenza.

Epidemiological Studies Difficult

The difficulties faced by epidemiologists in explaining trends in mortality rates from cardiovascular diseases are typical of the problems that occur in the statistical study of these diseases. Results from prospective studies, in which large groups of people are followed for years to see what characterizes those who develop cardiovascular diseases, as well as from comparisons of incidences of cardiovascular diseases among different populations, may sometimes vary from study to study in unexpected ways.

Gordon says that he and other epidemiologists tend not to believe any result until it has been repeated in several well-designed studies. Diabetes, high concentrations of serum cholesterol, cigarette smoking, and high blood pressure are correlated with risks of developing cardiovascular diseases in nearly all published studies. These conditions are thus accepted as risk factors by most investigators, even though a few studies may appear to exonerate one or another of them. Other factors, however, such as personality and lack of exercise, which have been implicated as risk factors in a few studies, are not accepted as proven independent risk factors by the vast majority of epidemiologists because most investigators have not found a relationship between these factors and cardiovascular disease.

In an ideal situation, the presence of a certain condition would virtually guarantee that a person will develop cardiovascular disease. The problem, though, is that cardiovascular diseases seem to have so many causes that this never occurs. Demonstrating cause and effect relationships is further complicated by the long latent period before cardiovascular disease becomes evident. Levy estimates that 2 to 5 decades can elapse before conditions that cause these diseases have their effects.

To further complicate matters, it has been impossible to execute an unbiased epidemiological study. For example, lack of compliance among members of populations is such that no one can hope to engage all of a randomly chosen sample of a population in a prospective study. Since people who go along with such studies are thought to have different characteristics than those who do not, no prospective study can be said to truly represent a particular population. But when the results of different prospective studies agree, as has often been the case in regard to the major cardiovascular risk factors, population sampling is less of a problem. It can be said that epidemiological studies, despite their limitations, have made it possible to predict, with a fairly high degree of accuracy, which groups of people are most likely to develop cardiovascular diseases. The susceptible groups can be identified on the basis of the risk factors that their members possess. A key question that then arises is, Can the susceptible individuals decrease their risk? Here the epidemiological evidence is equivocal, but some evidence exists that attempts to modify risk factors may pay off.

The risk factor that almost everyone agrees can be modified with beneficial results is high blood pressure. It is also one of the best predictors of cardiovascular disease, according to analyses of numerous prospective studies. For example, for participants in a prospective study of people in Framingham, Massachusetts, it was a better predictor than either cigarette smoking or serum cholesterol. Hypertension is generally defined as blood pressure greater than 160/95 mm-Hg.

Under this definition, the hypertensive men and women aged 45 to 74 who took part in this study had about three times as much coronary heart disease and over seven times the incidence of brain infarctions as did participants with normal blood pressures. Framingham partici-

pants with borderline hypertension, defined as blood pressures greater than 140/90 mm-Hg also experienced substantially increased incidences of cardiovascular diseases when compared to those with normal blood pressures. The incidences of these diseases among participants with mild hypertension were between those of participants with definite hypertension and with normal blood pressures. The Framingham results are supported by results from other prospective studies, all of which provide evidence that the risk of cardiovascular diseases increases with increasing blood pressure, even for blood pressures within the normal range.

Since 1950, drugs that significantly reduce high blood pressure have been available. Evidence that those who take these drugs may also decrease their risk of developing cardiovascular diseases comes from the Veterans Administration Cooperative Study on Hypertensive Agents coordinated by Martin Edwards Freis. Veterans (mainly middle-aged men) with definite hypertension who were treated had a significantly reduced incidence of stroke, heart failure, and renal failure than a similar group of veter-

Cardiovascular Disease and the Forms It Takes

Heart attack and stroke are the most spectacular—and lethal—manifestations of cardiovascular disease but they are usually the result of a long process of subtle deterioration of the circulatory system. A heart attack occurs when one or more of the three coronary arteries that supply blood to the heart muscle becomes blocked. This cuts off the supply of oxygen and other nutrients to a portion of the heart, which is thus damaged or killed. The damaged area of the heart muscle (myocardium) is called an infarct. Myocardial infarct, coronary occlusion, and coronary thrombosis (blood clot) are all synonyms for heart attack.

If the damage is so extensive that the heart cannot function, the individual dies. But even less severe damage may disrupt the electrical impulses that originate in the heart's internal pacemaker and regulate the heart beat. This will produce abnormal heart rhythms (cardiac arrhythmias). Certain of these are very dangerous because they may result in ventricular fibrillation; that is, the large chambers of the heart contract rapidly in an uncoordinated manner. Death may occur within minutes unless the normal heart rhythm is restored. Ventricular fibrillation can result from heart injuries or abnormalities other than blockage of the coronary arteries.

Sometimes heart attacks are caused by the trapping in the coronary arteries of a blood clot formed elsewhere in the body; usually, however, blockage of the arteries is the result of the formation of atherosclerotic plaques. The plaques develop gradually over a period of many years. They contain an accumulation of smooth muscle cells from the arterial wall, lipids, especially cholesterol, and calcium. (Atherosclerosis specifically refers to the development of these plaques in the arteries. Arteriosclerosis is a general term for the condition in which the arteries thicken and harden and lose their elasticity. Atherosclerosis is one type of arteriosclerosis.)

Atherosclerotic plaques serve as initiation sites for the formation of blood clots that block the arteries. In addition, the plaques may build up to the point where they partially block the coronary arteries so that the heart muscle gets enough oxygen when the individual is at rest but not during exertion. Transient pain results. This condition is called angina pectoris. The conditions characterized by inadequate supply of oxygen to the heart are collectively called coronary heart (or artery) disease. More than 4 million persons in the United States have a history of heart attack or angina pectoris.*

Atherosclerosis can affect and block any artery. If the lesions form in the arteries of the leg, blood flow to the extremity may be cut off, causing numbness, pain and ultimately gangrene if not treated. If the arteries blocked by atherosclerotic plaques are in the brain, stroke may result and a portion of the brain will be damaged. Alternatively, stroke may be caused when one of the blood vessels in the brain bursts. This kind of stroke is most likely to occur in persons who have uncontrolled high blood pressure, especially if they also have atherosclerosis. About 1.8 million persons have suffered strokes, which cause about 200,000 deaths a year in this country.

High blood pressure, also called hypertension, is a major risk factor not just for stroke but also for heart attack and atherosclerosis. Hypertension does not produce symptoms unless it is severe or has been untreated for a long time. But it puts a strain on the heart, which is forced to work harder in order to move the blood against higher than normal pressures. An enlarged heart is one result of high blood pressure. Hypertension may also contribute to the development of atherosclerosis by damaging arterial walls. Kidney failure is another consequence of prolonged, elevated blood pressures. Almost 24 million persons have high blood pressure—and only about 30 percent of them have it adequately controlled even though it is easy to detect and effective therapies are available.

Rheumatic heart disease usually afflicts children between the ages of 5 and 15. It often begins with a severe throat infection caused by streptococcal bacteria (strep throat). A small percentage of infected persons make antibodies against the bacteria that also attack and damage the heart valves and muscle with the result that blood can no longer be effectively pumped. Mortality from rheumatic fever has decreased because antibiotics can control strep infections, and diseased valves can be surgically repaired. But approximately 13,500 people still die every year as a result of rheumatic heart disease.

Congenital defects also contribute to the toll from cardiovascular disease. About 25,000 infants are born every year with defects of the heart or major blood vessels. Some of these are the result of rubella infection of the mother during the first 3 months of pregnancy. Vaccination programs have contributed to a decrease in the number of these defects. Other defects are of unknown origin, but many can now be corrected surgically.

Congestive heart failure occurs when the heart has been weakened, whether by high blood pressure, heart attack, rheumatic heart disease, or birth defects, and pumps well below its normal capacity. Loss of pumping power causes fluid to accumulate in the abdomen, legs, and lungs, which makes breathing difficult. Congestive heart failure can be effectively treated with drugs.—J.L.M.

*All of the figures cited in this article are taken from the 1977 edition of the *Heart Facts* pamphlet, to be published by the American Heart Association.

ans who did not take the drugs. Although the population in this study is not representative of the subpopulation in the United States that has high blood pressure (for example, women, who are more prone than men to develop hypertension, are not represented), results lead most researchers to conclude that antihypertensive drugs are highly effective in reducing risks of cardiovascular diseases.

Cigarette smoking has repeatedly been shown to substantially increase the risk of cardiovascular disease, and there is some evidence that those who stop smoking may decrease their risk. The Framingham study indicates, for example, that men who smoked at the beginning of the study and subsequently stopped had only half as many heart attacks after 18 years as those who continued to smoke.

Two studies far larger than the Framingham study led to similar conclusions about the effects of giving up cigarettes. About 300,000 U.S. veterans were studied for 8.5 years by Eugene Rogot and his associates at NHLBI. They found that the mortality rates of cigarette smokers were 1.6 times those of nonsmokers. The risk was related to the number of cigarettes smoked. For example, persons who smoke more than 40 cigarettes per day and are between the ages of 30 and 34, have increased their risk almost threefold. The risk for those who stopped smoking decreased with the time since they last smoked.

A second large-scale study was undertaken by the ACS under the direction of E. Cuyler Hammond. These investigators monitored over 1 million people for 6 years by questionnaires. The results indicated that the mortality rate from coronary disease for those who had smoked more than 20 cigarettes a day and stopped for at least 20 years was almost that of those who had never smoked. There are problems in the design of these studies, but since they all lead to similar conclusions, most investigators believe that the results apply to the population at large.

Changes in serum cholesterol concentrations and their effects on the risk of developing cardiovascular diseases are just as difficult to study as changes in blood pressure or smoking habits. One unresolved question is, Can serum cholesterol concentrations be safely, easily, and effectively decreased by drugs? Some drugs are available, but it is not clear whether it is safe to take them for long periods of time or whether they are effective. A clinical trial designed to see whether these drugs can effectively lower serum cholesterol concentrations and decrease incidences of heart disease in a select group of men is now under way (*Science*, 21 November 1975), but the results will not be available for years.

Diet alone has often been suggested as a means of reducing serum cholesterol concentrations and, possibly, the risk of cardiovascular disease, but epidemiological studies are not sufficient to support the hypothesis that changes in diet decrease the risk. In most studies in which investigators have tried to determine whether a low-fat, low-cholesterol diet does decrease blood cholesterol concentrations and the risk of coronary heart disease, only modest—approximately 10 percent—reductions in blood cholesterol have been observed; the data were not adequate to show whether this affected coronary mortality. In fact, there is no consensus among researchers as to whether the evidence that diet affects serum cholesterol concentrations and subsequent risks of cardiovascular disease is strong enough that most people in the United States should be persuaded to modify what they eat. One problem with advocating diets low in saturated fats and cholesterol is that many people will substitute carbohydrates for fats. But high carbohydrate diets have adverse effects on some people.

Diet and the Risk of Heart Disease

Epidemiological evidence that diet affects serum cholesterol concentrations and risk of heart disease is usually impossible to obtain from studies of any one population. The people of any country often vary so little in their dietary habits that it cannot be demonstrated that those who develop heart disease eat different foods from those who do not develop heart disease. However, people of different countries do vary substantially in their eating habits and do experience different rates of heart disease. This was illustrated by several studies, including the International Cooperative Study on the Epidemiology of Cardiovascular Disease, a prospective study of 18 population samples in seven countries—Finland, Greece, Italy, Japan, the Netherlands, the United States, and Yugoslavia.

In that study, investigators compared the incidence of heart disease among 12,000 men between 40 and 59 years of age at the beginning of the study, who were studied for 10 years. Mean rates of heart disease varied fourfold with the highest rates in the United States and Finland and the lowest in Japan. The rates were significantly correlated with the serum cholesterol concentrations and also with the saturated fat intake of the populations. Other components of the diets, which included total calories, total fat, monounsaturated fat, polyunsaturated fat, and total protein, were not significantly correlated with incidences of heart disease.

Since different populations have different genetic backgrounds and different habits, the independent effects of diet and cholesterol are hard to assess. This is a problem that applies to all studies that examine relationships between diet, cholesterol, and heart disease. Those who advocate changes in diet generally do not say that epidemiological evidence proves that diet will be effective. Instead, they draw on biochemical studies of heart disease in animals and in humans to support that contention.

Several investigators have shown that when primates and other laboratory animals are fed diets high in saturated fats and cholesterol they develop plaques that resemble atherosclerotic plaques in humans. Although this does not prove that the same thing happens in humans, Stamler cautions against supposing that humans are different from all other animals, including primates. It may be significant that certain genetic disorders in people produce very high concentrations of serum cholesterol and coronary heart disease at an early age. These disorders cannot yet be successfully treated by diet therapy, but they do demonstrate that a very high concentration of serum cholesterol is associated with heart disease. While all admit that no one piece of evidence by itself proves anything, many investigators believe that all the evidence considered together shows a plausible, if not certain, link between diet, serum cholesterol, and heart disease.

The problems with obtaining convincing epidemiological evidence that changes in blood pressure, smoking habits, or serum cholesterol concentrations can change the risk of developing cardiovascular diseases are difficult enough; but the problems involved with investigating the effects of changes in other habits are even more difficult. For example, most researchers believe that those who exercise have decreased their risk of developing cardiovascular disease but have been unable to demonstrate it.

Epidemiology has suggested possible causes of cardiovascular diseases rather than proved that various conditions cause these diseases. These suggested causes may be further investigated by biochemists and clinicians who are attempting to paint a general picture of the causes and pathogenesis of cardiovascular diseases, with the hope that prevention, amelioration, or even cure may follow.—GINA BARI KOLATA and JEAN L. MARX