227. L. O. Werme, J. Nordgren, H. Ågren, C. Nordling, K. Siegbahn, *Z. Phys.* **272**, 131 (1975).
228. J. Nordgren, H. Ågren, L. O. Werme, C. Nordling, K. Siegbahn, *J. Phys. B* **9** (No. 2), 295 (1976).
229. J. Nordgren, H. Ågren, L. Selander, C. Nordling, K. Siegbahn, paper presented at the Nordic Symposium on Atomic and Molecular Transition Probabilities, Lund, 28 and 29 March 1977.
230. J. Nordgren, H. Ågren, C. Nordling, K. Siegbahn, *Ann. Acad. Regiae Sci. Ups.* **21**, 23 (1978).
231. H. Ågren, J. Nordgren, L. Selander, C. Nordling, K. Siegbahn, *Phys. Scr.* **18**, 499 (1978).
232. J. Nordgren, H. Ågren, L. Pettersson, L. Selander, S. Griep, C. Nordling, K. Siegbahn, *ibid.* **20**, 623 (1979).
233. H. Ågren, L. Selander, J. Nordgren, C. Nordling, K. Siegbahn, J. Müller, *Chem. Phys.* **37**, 161 (1979).
234. L. O. Werme, thesis, *Acta Universitatis Upsaliensis* **241** (1973).
235. J. Nordgren, thesis, *ibid.* **418** (1977).
236. H. Ågren, thesis, University of Uppsala (1979).
237. K. Siegbahn, *Phys. Scr.* **16**, 167 (1977).
238. B. Wannberg and A. Sköllermo, *J. Electron Spectrosc.* **10**, 45 (1977).
239. *Philos. Trans. R. Soc. London* **268**, 1 (1970).
240. D. A. Shirley, Ed., *Electron Spectroscopy* (North-Holland, Amsterdam, 1972).
241. *Faraday Discuss. Chem. Soc.* **54** (1972).
242. W. Dekeyser *et al.*, Eds., *Electron Emission Spectroscopy* (Reidel, Dordrecht, 1973).
243. R. Caudano and J. Verbist, Eds., *Electron Spectroscopy* (Elsevier, Amsterdam, 1974).
244. *Faraday Discuss. Chem. Soc.* **60** (1975).
245. J. Hedman and K. Siegbahn, Eds., *Phys. Scr.* **16** (Nos. 5–6) (1977).
246. *J. Electron Spectrosc.* **15** (1979).
247. A. D. Baker and D. Betteridge, *Photoelectron Spectroscopy* (Pergamon, Oxford, 1972).
248. J. H. D. Eland, *Photoelectron Spectroscopy* (Butterworths, London, 1974).
249. T. A. Carlson, *Photoelectron and Auger Spectroscopy* (Plenum, New York, 1975).
250. C. R. Brundle and A. D. Baker, Eds., *Electron Spectroscopy* (Academic Press, New York, vol. 1, 1977; vol. 2, 1978; vol. 3, 1979; vol. 4, 1981).
251. D. Briggs, Ed., *Handbook of X-ray and Ultraviolet Photoelectron Spectroscopy* (Heyden, London, 1977).
252. J. W. Rabalais, *Principles of Ultraviolet Photoelectron Spectroscopy* (Wiley-Interscience, New York, 1977).
253. P. K. Ghosh, *A Whiff of Photoelectron Spectroscopy* (Swan, New Delhi, 1978).
254. B. Feuerbacher, B. Fitton, R. F. Willis, Eds., *Photoemission and the Electronic Properties of Surfaces* (Wiley-Interscience, New York, 1978).
255. M. Cardona and L. Ley, Eds., *Photoemission in Solids, Topics in Applied Physics* (Springer-Verlag, New York, 1978 and 1979), vols. 26 and 27.
256. M. W. Roberts and C. S. McKee, *Chemistry of the Metal-Gas Interface* (Clarendon, Oxford, 1978).
257. R. E. Ballard, *Photoelectron Spectroscopy and Molecular Orbital Theory* (Hilger, Bristol, 1978).
258. J. Berkowitz, *Photoabsorption, Photoionization and Photoelectron Spectroscopy* (Academic Press, New York, 1979).
259. H. Siegbahn and L. Karlsson, in *Handbuch der Physik*, vol. 31, *Photoelectron Spectroscopy*, W. Mehlhorn, Ed. (Springer-Verlag, Berlin, in press).
260. ———, *Electron Spectroscopy for Atoms, Molecules and Condensed Matter* (North-Holland, Amsterdam, in press).

Cardiovascular Research: Decades of Progress, a Decade of Promise

Robert I. Levy and Jay Moskowitz

Summary. Mortality due to cardiovascular diseases has decreased more than 30 percent in the last 30 years, and this decline has accelerated so much that over 60 percent of it has occurred between 1970 and 1980. The past and present contributions of advances in cardiovascular research to this decline are reviewed. Although there have been significant research accomplishments, too many people still die of heart and blood vessel diseases. Continued emphasis must be placed on research in the areas of etiology and pathogenesis, on validating potentially beneficial research hypotheses, and on the translation and dissemination of research results to the health care practitioner and the public. Only then can our long-term goal, the prevention of cardiovascular disease, be fully realized.

Heart and blood vessel diseases have been the major cause of death in the United States for more than 40 years and account for over half of all deaths (Fig. 1). The magnitude of the health care problem caused by these diseases cannot be overemphasized. Each day, an estimated 3400 Americans, more than two each minute, suffer a heart attack (*1*, *2*). Each day, approximately 1600 people suffer strokes. Some 25,000 children are born with defective hearts every year, and there are over 100,000 children and 1.7 million adults who suffer from rheumatic heart disease (*1–3*).

The leading cause of death in the United States is coronary heart disease, which accounts for two-thirds of all cardiovascular deaths. It alone was responsible for nearly 650,000 deaths in 1978, and more than 150,000 of these occurred in people less than 65 years old. Approximately one-third of the deaths from all causes in persons between the ages of 35 and 64 years are due to coronary heart disease, and nearly 40 percent of all deaths in white males aged 55 years and over are caused by this disease (*4*). In contrast, all forms of cancer combined (the second leading cause of death) were responsible for nearly 400,000 deaths in the United States in 1978 (*5*). Cardiovascular diseases have led the list of the nation's killers for more than half a century, and they remain so today despite a steady decline in heart disease death rates since the 1950's (Fig. 2). The social and economic toll of diseases of the heart and blood is equally severe. In fact, cardiovascular disease accounts for more bed days than any other single condition. The total economic cost of cardiovascular disorders is estimated to be in excess of $60 billion annually (*6*). Of this amount, $20 billion represents health expenditures, $10 billion productivity lost due to illness, and $30 billion potential productivity lost due to early death (*6*). This $60 billion accounts for more than one-fifth of the total cost of illness in the United States.

Magnitude of Decline in Mortality from Cardiovascular Diseases

Cardiovascular mortality has decreased more than 30 percent in the last 30 years, and this decline has accelerated so much that over 60 percent of it has occurred between 1970 and 1980 (*5*) (Fig. 2). Among people between 25 and 44 years of age, deaths as a result of heart disease have declined from first to third

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among all causes but remain the leading cause of death at ages 45 and over. Although male death rates for coronary heart disease exceed those for females, more women than men die from stroke (*1*, *2*). The decline in cerebrovascular death rates has been even greater than that from coronary heart disease. Moreover, the pattern of decline differs (Fig. 3). The decline in stroke began earlier in the century and has accelerated during the past decade. Since 1972, stroke-related deaths have declined by 5 percent a year (over 40 percent) with the greatest decline experienced among black females (*4*).

In 1978, rates of death from coronary heart diseases and cerebrovascular diseases varied among the 50 states. The highest rates occurred in the southeastern states; the lowest in the Rocky

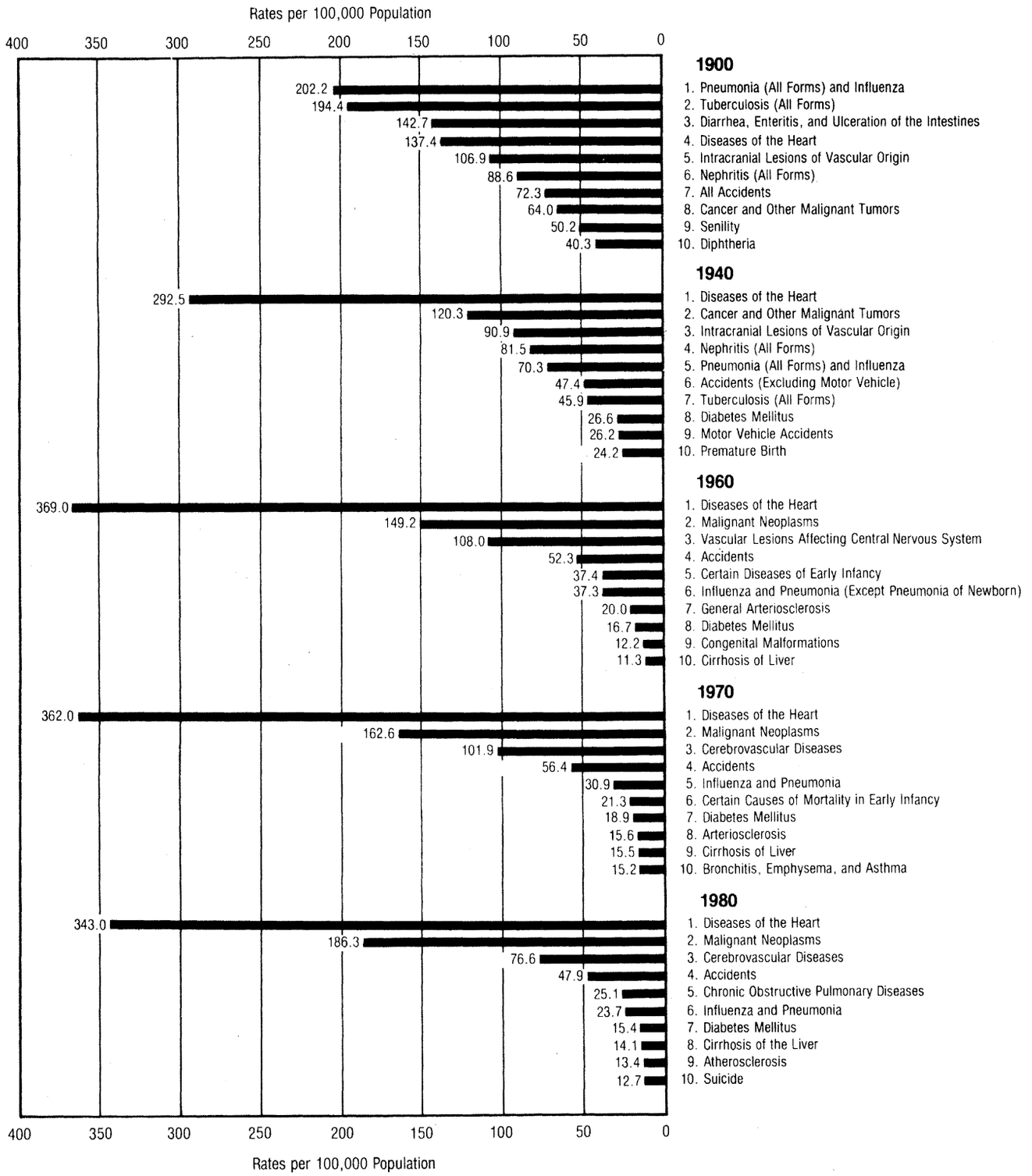

Fig. 1. The ten leading causes of death in the United States. Death rates are shown for 1900, 1940, 1960, 1970, and 1980. The terminology is that used in the edition of *International List of Causes of Death* in effect at that time. The data for 1900, 1940, and 1960 are from (*65*); data for 1970 are from (*66*); data for 1980 are from (*67*). Malignant neoplasms (No. 2 in 1960, 1970, and 1980) include neoplasms of lymphatic and hematopoietic tissue.

Mountain states (Fig. 4). The same pattern is observed for stroke (*7, 8*).

Other industrialized countries have not experienced the same pattern of change in mortality from coronary heart disease as the United States. In a few, such as Australia, Japan, and Canada, the decreases have been appreciable, but less than those for the United States. In contrast, many countries such as Romania, Poland, Northern Ireland, and West Germany have reported increases in mortality rates from coronary heart disease (*9*).

The decline in overall cardiovascular mortality is associated with more than 1.2 million lives being extended between 1968 and 1978. Though it is often noted that life expectancy in the United States has not changed dramatically since the turn of the century despite the control of infectious diseases and numerous advances in biomedical research, the fact is that since the decline in cardiovascular diseases there has been a striking increase in life expectancy. Both men and women have gained more than 2 years over the last decade (*10*). These gains have been most striking in black males and females for whom there has been an increase of more than 3½ years of life expectancy in the last 10 years (*11*).

Why the Decline in Coronary Heart Disease and Stroke Mortality?

Many factors may be responsible for the decline in mortality from coronary heart disease and stroke, including improved medical services, the development of coronary care units, advances in surgical and medical treatment of coronary heart disease, and improved control of blood pressure. Socioeconomic and environmental factors may also be responsible, such as changes in life-styles, less smoking, increased leisure time activity, and modifications in eating habits (*12*).

Changes in coronary care have been cited as having a significant impact on the rate of decline in cardiovascular disease mortality. Since 1963, when the first coronary care unit was organized in the United States, specialized hospital care—including early noninvasive diagnostic techniques, sophisticated treatment regimens, and prevention protocols—has become standard for heart disease patients (*13*). Changes in American life-style and in personal coronary disease risk factors are another identified explanation for the decline (*14*). There has been evidence that awareness and effective treatment of hypertension has increased dramatically in the last decade (*15*). Positive changes in nutritional habits in recent years are evidenced by decreases in the consumption of cholesterol and saturated fats (*14, 16*). The number of cigarette smokers and the amount of tar and nicotine in cigarettes have dropped considerably since the release of the first Surgeon General's report on smoking in 1964 (*17*). Exercise as a leisure habit, in particular, jogging, has increased in frequency (*18, 19*).

Although there is general agreement that the decline in coronary heart disease mortality is real, the probable cause or causes for this decline cannot be easily identified. In fact, there are too many potential causes rather than too few. Advances have occurred, however, in the understanding of the etiology of cardiovascular diseases as well as in their prevention, diagnosis, and treatment.

To review systematically the advances that may have contributed to the decline in cardiovascular mortality, we discuss here ten major areas of cardiovascular disease research. Four areas focus on major etiological processes: arteriosclerosis, hypertension, congenital and rheumatic heart disease, and cardiomyopathies and infections of the heart. Three areas are concerned with clinical syndromes resulting from these basic processes: coronary, peripheral, and cerebrovascular disease. Two areas are concerned with sequelae of these problems: arrhythmias and heart failure and shock. The last area is concerned with circulatory assistance, the artificial heart, and heart transplantation.

Etiological Processes

Arteriosclerosis. In 1970, 87 percent of the more than 1 million deaths in the United States due to heart and blood vessel diseases were attributable to arteriosclerosis and its sequelae (*3*). At that time, as now, the causes of atherosclerosis (*20*), the most common form of arteriosclerosis, were not well understood. Atherosclerosis could not be diagnosed effectively and there was no clinical therapy to control or reverse plaque development. In 1971, a Task Force on Arteriosclerosis was established by the federal government to assess research needs and make recommendations on priorities for future program plans in this area (*21*).

Most of the recommendations of the task force have been implemented in the past decade and important advances have been realized in fundamental and clinical research on arteriosclerosis. Several clues, however, had been dis-

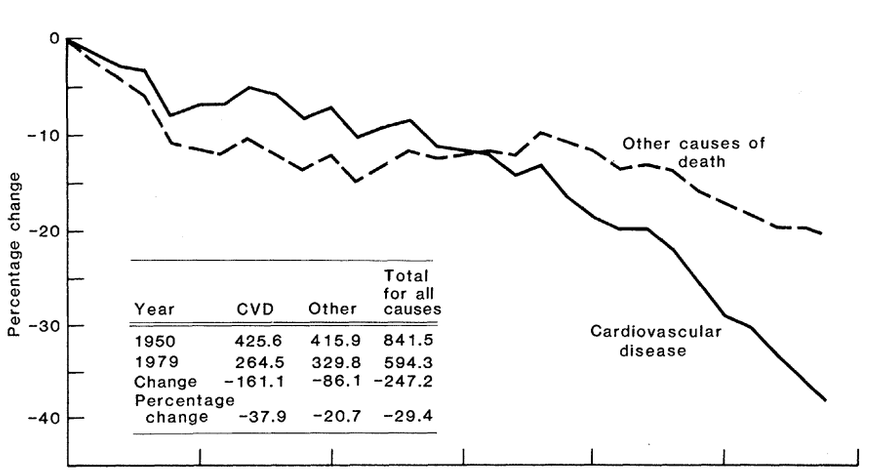

Fig. 2. Trends in cardiovascular disease and noncardiovascular disease. The inset, with data age-adjusted to the U.S. population in 1940, shows the percentage change from 1950 to 1979. Cardiovascular disease here excludes congenital heart disease. Data for 1979 are NHLBI estimates.

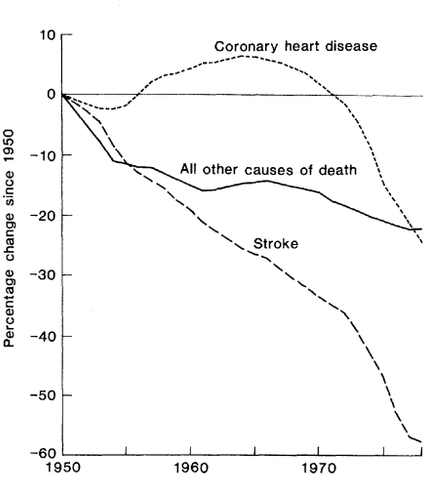

Fig. 3. Percentage change in death rates since 1950 for coronary heart disease, stroke, and all other causes, for people aged 35 to 74 years in the United States, 1950 to 1978.

covered previously from population-based epidemiological studies. On the basis of statistical associations, three major risk-treatable factors had been identified, including elevated blood cholesterol levels, high blood pressure, and cigarette smoking. A number of additional factors were also recognized, such as diabetes, physical inactivity, obesity, age, male sex, and certain personality types, that is, coronary-prone behavior (*8, 22*). In the last 10 years, there has been a growing awareness that atherosclerosis is not a disease confined to older people or to men; women and young people are also at risk (*23*). The theory that atherosclerosis begins during childhood and continues to develop through adulthood has begun to receive considerable attention (*24*).

Research in cell and molecular biology has provided new information about components of the blood and the arterial wall and their interactions (*8*). The use of cell cultures has made it possible to examine the interactions between blood components, such as the lipoproteins, platelets, macrophages, and hormones, and the individual cells of the arterial wall, including the endothelium, and to assess conditions that promote or reverse atherogenesis (*25*). Cell culture techniques have also made it possible to identify inherited cellular abnormalities that lead to atherosclerosis, to define cellular pathways involved in lipoprotein removal and catabolism, and to identify factors that regulate the growth of arterial cells. The importance of cholesterol-carrying lipoproteins and their apoproteins has been clarified during the last decade. The relation of the lipoproteins to other risk factors, such as hypertension, physical inactivity, smoking, and diabetes has become better understood.

Recent findings have focused attention on the high-density lipoproteins (HDL's), which are a negative risk factor. Unlike the atherogenic low-density lipoproteins (LDL), HDL's have been inversely associated with coronary heart disease risk. Moreover, the negative correlation between HDL cholesterol and coronary heart disease is independent of other risk factors. Increasing epidemiologic evidence supports the hypothesis that increased concentrations of HDL may be a protective factor in the development of atherosclerosis. Levels of HDL have been correlated positively with exercise and moderate ingestion of alcohol and inversely related to obesity, smoking, poor control of diabetes, and the use of progestin-containing contraceptives (*26, 27*). The cause and effect of the inverse relation between HDL and coronary heart disease, however, remains unclear (*28*).

The participation of platelets in thrombosis has recently been more clearly defined. Mechanisms have been described by which platelets are stimulated to adhere and aggregate and to release their granular contents. This knowledge has led to the development of methods for identifying the involvement of platelets in thrombosis and to new attempts to inhibit the undesirable aspects of platelet function, and thereby prevent thrombosis. One of the most important discoveries in the last 10 years has been that of the role of the prostaglandins in arterial wall metabolism (*29*). These compounds strongly influence the behavior of the arterial wall and the cells in the blood transversing the arterial lumen. Prostaglandin derivatives, particularly thromboxane A_2 and prostacyclin (PGI_2), are thought to be the most potent substances known for aggregating and dispersing platelets (*30*). An unbalance in thromboxane A_2 and PGI_2 may control the process of thrombosis and perhaps atherosclerosis at the arterial cell surface (*31*). Studies show that secreted platelet granule proteins enter the vessel wall and affect its metabolism, and that PGI_2 infusion can block platelet adhesion to the same vessel wall. These studies may lead to a means for monitoring and preventing platelet interactions with injured vessels that might otherwise cause ath-

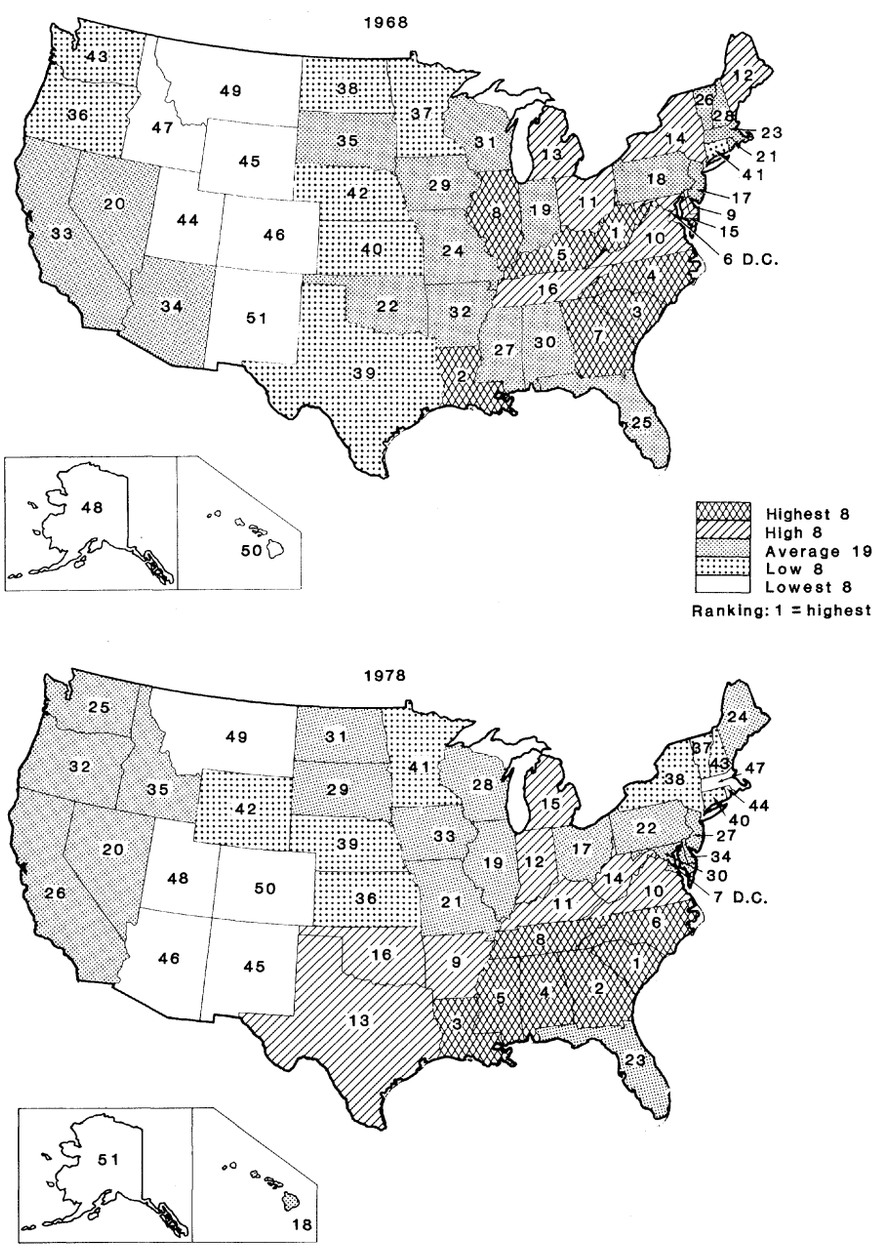

Fig. 4. Rank distribution by state of coronary heart disease (ICDA Code 410-414) shown by mortality rates for the total population aged 35 to 74 years, 1968 and 1978.

erosclerotic vascular disease. Some long available medications recently shown to modify prostaglandin metabolism, such as aspirin and dipyridamole, are now being examined for their potential in preventing the complications of atherosclerosis (*32*).

A major contribution of the 1970's has been the enhancement of our ability to diagnose atherosclerosis effectively. The introduction and availability of such techniques as ultrasound, x-ray densitometry, and computer-assisted image-enhancement techniques set the stage for improved and earlier diagnosis of atherosclerosis and ischemic heart disease. These new techniques have allowed physicians to detect directly the presence of often asymptomatic plaque in the large vessels of the neck and thigh as well as to measure indirectly coronary atherosclerosis through observation of metabolism and the segment movement of the left ventricular wall during exercise as well as at rest (*33*).

Hypertension. In 1948, when the National Heart Institute first came into being, there was little research in hypertension and physicians had little to offer hypertensive patients. The few drugs available either were largely ineffective or had serious side effects. The major therapeutic alternative for the hypertensive was the rice diet, which was effective in some patients but quite unpalatable to most. Physicians were not always sure, when treating hypertension, whether they were dealing with a disease, a symptom of a disease, or a possible beneficial circulatory adaptation to the aging process. In fact, a theory in vogue in the late 1950's was that hypertension was essential to the maintenance of critical perfusion pressures in areas such as the brain. This concept suggested that more harm than good would occur if blood pressure was lowered in individuals with hypertension.

Much has been learned about the involvement of the central and peripheral nervous systems in the control of blood pressure (*34, 35*). The role of previously obscure hormones, such as the kallikreins and kinins, and of the prostaglandins and renin and angiotensin, is being unraveled. Renin and angiotensin are clearly involved in the regulation of blood pressure. For some time, inhibitors of these substances have been used to investigate blood pressure disorders. In the early 1970's two types of inhibitors of the renin-angiotensin system became available for clinical research, but both had shortcomings, such as the inability to be used for chronic blockade, inherent agonist properties, or stimulatory effects on circulating bradykinin. These shortcomings, however, helped researchers gain additional insight into the functions of the renin system, although the precise role of renin in clinical hypertension remains obscure (*36*). Recently, Captopril, an orally active inhibitor of the angiotensin-converting enzyme, has been developed. This octapeptide inhibits the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. This new means of controlling high blood pressure may provide new insights into the pathophysiology of the disease (*37*).

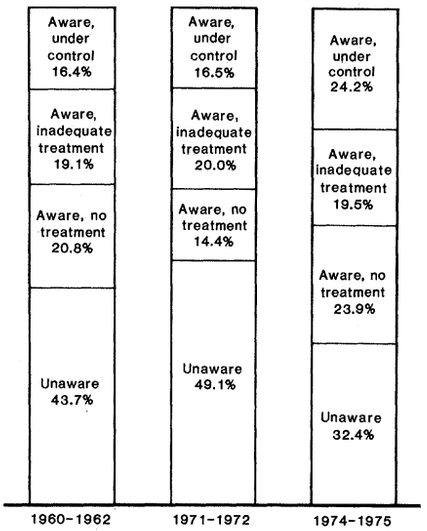

Fig. 5. Percentage of patients with hypertension in specified awareness, treatment, and control status categories in the United States. People with hypertension are those with a blood pressure of ≥ 160/95 mmHg or who take medicine for high blood pressure.

In early 1970, the Veterans Administration collaborative study (*38*) reported a clinical trial that demonstrated the benefits of treating moderate and severe hypertension. It was found that good blood pressure control could be achieved and maintained with the drugs used during these trials and that adequate treatment prevented stroke, renal, and heart failure. Recently, it has been suggested that even mild hypertension should be treated and that such treatment might serve to prevent such sequelae as stroke, heart failure, renal failure, and heart attack (*39, 40*).

There is evidence of substantial progress in controlling high blood pressure. Illness and premature death associated with the condition are declining. This decline has accelerated during the past decade concurrent with a national program to control high blood pressure (*14*). In 1972, the Department of Health, Education, and Welfare initiated the National High Blood Pressure Education Program (NHBPEP), which has been coordinated by the National Heart, Lung, and Blood Institute (NHLBI). The program's goal was to make the public aware that high blood pressure is common, often asymptomatic, and treatable but can lead to serious health problems (*6*). As a result of the activities of the NHBPEP, many people have entered programs for treatment. Surveys indicate that awareness of hypertension is markedly higher now than it was in the 1960's (Fig. 5). In addition, the number of people going to physicians for advice on hypertension has increased since 1972. It is estimated that there may now be more than 10 million Americans on effective blood pressure control regimens (*14*). Concomitant with this increase in awareness and control has been a decline in mortality for diseases associated with hypertension, notably coronary heart disease, stroke, and malignant hypertension (*9*).

Congenital and rheumatic diseases. Notable advances have also been made in the prevention of congenital heart disease. An effective rubella vaccine has reduced the number of infants born with rubella-caused congenital heart disease. The incidence of congenital heart disease resulting from Down's syndrome has decreased, and this can be attributed to two factors: older women are having a smaller proportion of all babies, and earlier diagnosis in utero is now possible with some forms of congenital heart disease associated with chromosomal abnormalities. Alcohol, anticonvulsants (trimethadione), and certain drugs (lithium) have also been implicated as causative agents for congenital heart disease.

Open heart surgery, made possible by the development of the heart-lung machine in the early 1950's, has revolutionized heart surgery. Using hypothermia, the heart-lung machine, and cardioplegia, surgeons have found it possible to correct heart malformations in infants and newborns and to repair or modify even the more complicated congenital defects (*12*). The availability of multiple forms of heart valve prosthesis has helped reduce the toll of rheumatic heart disease. Recent research on the immunologic concomitants of certain streptococcal infections holds promise for eventual prevention of this disease through vaccination.

New noninvasive technologies, such as echocardiography, have gained prominence as means of diagnosing and determining heart defects in the fetus in utero and in the newborn and have now been used effectively to follow congenital disease in older children and adults. With

such devices as real-time sector scanners, the spatial locations of the chambers of the heart and the major heart valves can be visualized. With this new equipment it is often possible to determine how the heart valves are functioning as well as to identify which chambers of an infant's heart are enlarged, and how the enlargement responds to medical treatment.

Tests are now being conducted (*41*) on the effectiveness of prostaglandin inhibitors for the treatment of such common conditions as patent ductus arteriosius. In this congenital abnormality of many premature infants, the vessel connecting the pulmonary artery to the aorta fails to close.

Cardiomyopathies and infections of the heart. Ten years ago, cardiomyopathies were not easily recognized nor was there available solid evidence to document their actual incidence, prevalence, and geographic distribution. While the causes of most cardiomyopathies still remain obscure, diagnosis is easier and a number of factors have been identified as causative agents. For example, alcohol has been identified with a toxic cardiomyopathy; its effect on heart muscle function and structure is now better understood. The role of certain viral diseases and some forms of myocarditis have also been made clearer, and genetic predisposition to some cardiomyopathies have been demonstrated through clinical and animal studies (*42*). Improvements in noninvasive diagnostic instrumentation have led to increased frequency in recognition of certain cardiomyopathies. Detailed studies have helped scientists identify and characterize the mechanical behavior of muscle during contraction and relaxation and to relate these events to physiological, biochemical, and morphological aspects of the heart. Great progress has been shown in the understanding of the structure of proteins that constitute the contractile and regulatory processes of the heart muscle.

Clinical Syndromes

Coronary heart disease. In the recent past, information was available on many aspects of the causes, diagnosis, and treatment of coronary heart disease. There was a need, however, for further research to resolve basic unanswered questions, one of which was why coronary heart disease ultimately manifests itself as heart attack, angina, or sudden death. While it was clear that ventricular fibrillation, a chaotic disturbance of the heart rhythm, is often the final stage before sudden death, no drugs or other effective treatments were available to prevent this condition except under intensive medical care in the hospital setting. The high frequency of out-of-hospital deaths from coronary heart disease contrasted sharply with lives saved through in-hospital systems and emergency cardiac care. This difference highlighted the need for improved methods to control arrhythmia and achieve cardiac resuscitation in emergency situations outside hospitals. More research, both clinical and fundamental, is critical to developing a better understanding of the cause and course of coronary heart disease and for improving diagnosis and treatment. The 1970's saw progress in the diagnosis of heart disease by tests that are of low risk to the patient. These so-called noninvasive diagnostic techniques include echocardiography, low activity radioactive tracers, and computerized tomographic x-ray techniques (*43*). Echocardiography provides an assessment of heart anatomy by using reflected sound waves from the heart and great vessels. This technique, in general use across the country, allows diagnosis to be made in several situations that in the past were either uncertain or required cardiac catheterization. Several radiopharmaceuticals, such as technetium 99m and thallium-201, have been used in the clinical assessment of infarct size, myocardial perfusion, and ventricular function (*44*). Computerized tomographic x-ray techniques have been used to determine the success of implanting coronary artery grafts into the diseased vessel.

Each year, 100,000 coronary bypass operations for the treatment of coronary heart disease are performed in the United States. In 1972, a prospective randomized study was initiated to compare medical therapy with coronary bypass surgery for the immediate management of patients with unstable angina pectoris. The results obtained between 1972 and 1976, with 288 patients randomly assigned to drug therapy or surgery, indicate that patients with unstable angina pectoris who receive intensive medical therapy—including the administration of propranolol and long-acting nitrates in pharmacological doses—report adequate control of pain and show no increase over surgical controls in early mortality or myocardial infarction rates (*45*). Surgical techniques for coronary bypass surgery are improving. A large-scale collaborative clinical trial—the Coronary Artery Surgery Study (CASS)—designed to assess the effects of coronary artery bypass surgery on morbidity and mortality in patients with chronic coronary heart disease, has been initiated by the NHLBI (*46*).

Recently, a less invasive and less costly therapeutic alternative to coronary bypass surgery has become available for a limited subset (5 to 10 percent) of these patients. The technique, percutaneous transluminal coronary angioplasty (PTCA), was introduced as a clinical therapy in 1977 by Andreas Gruntzig [see (*47*)]. He had previously perfected a double-lumen balloon dilating catheter for use in the treatment of peripheral obstructive vascular disease. This technique quickly received widespread interest by cardiologists treating patients with ischemic heart disease. Since the introduction of PTCA as a clinical therapeutic approach, there has been a marked improvement in the guiding catheters, the balloon dilation catheters, and the inflation device (*47*). There is no doubt that proximal, noncalcified, partially occluded vessels can be dilated by this new technique with associated disappearance of angina (*48*). The long-term efficacy of the procedure still remains to be determined.

Immediate infusion of thrombolytic agents by catheter at the point of coronary occlusion has been proposed as a new procedure for the prevention or limitation of heart infarct size. Thrombus (clot) formation may occur during the initial stages of myocardial infarction. Efforts to break up the clots, with such agents as streptokinase, may prove useful in restoring blood flow and in reducing the extent of myocardial injury if they are used early enough. This, however, must be established through clinical trials. Multiple interventions developed within the last decade have been shown to be effective in limiting infarct size and in decreasing myocardial ischemic injury in animal studies. To date, however, no treatment has been proved so efficacious in humans that its routine use can be recommended (*49*). Nevertheless, some of these interventions, such as β-adrenergic blockade, intravenous nitroglycerin, glucose-insulin potassium infusion, and intracoronary thrombolysis, are promising.

Research on sudden cardiac death continues to provide insights on circumstances under which chronic coronary heart disease leads to heart attack and death. Today, the wider, more effective, implementation of emergency medical systems, including cardiopulmonary resuscitation, is saving lives that otherwise would be lost to out-of-hospital deaths (*50*).

Basic research on ion fluxes across cardiac cell membranes is concerned with the possible association of "slow" calcium current with certain arrhythmic disturbances. Recent research has emphasized a central role for calcium in smooth muscle function. Calcium ions are involved in electrophysiologic processes, link excitation to muscular contraction, control energy storage and utilization, and constrict vascular smooth muscle in coronary and systemic arteries. A new group of pharmacologic agents that block the passage of calcium ions across cell membranes has recently been developed (*51*). These agents appear to act during the slow inward current of cellular depolarization. The most extensive clinical experience has been obtained with four of these agents: verapamil, nifedipine, perhexiline, and diltiazem. Verapamil, for example, has profound electrophysiologic effects and is emerging as a valuable agent for certain arrhythmias. Some of these drugs are of particular value in angina pectoris, cardiomyopathy, and hypertension. Further research on the role of calcium ions on electrophysiologic processes and the influence of these drugs on the heart may have significant implication for cardiovascular medicine.

Peripheral vascular diseases. Surgeons have developed techniques to replace large intrathoracic and intra-abdominal artery segments with vascular or prosthetic grafts but little attention had been paid to research on disorders of the veins or of the medium or smaller branch vessels of the large arteries. Little was understood of the mechanisms that might lead to peripheral vascular disease other than arteriosclerosis and more information is needed on improved diagnosis, therapy, and rehabilitation of patients.

During the past 10 years, improvements have been made in assessing the severity of peripheral arterial diseases with the use of new ultrasonic, radioisotopic, and radiographic techniques. The ability to replace or bypass irreversible obstructive lesions in large, main arteries has increased markedly, and research has also improved the use of such therapies for medium and small-size vascular arteries. Reductions in the incidence of venous embolism may now be achieved through carefully controlled low-dose heparin therapy which is given before surgery and during the recovery phase until the patient is ambulatory (*52*).

Cerebrovascular disease. Hypertension, arteriosclerosis, and diabetes have long been recognized as major risk factors for the development of cerebrovascular disease. To predict, ameliorate, and eventually prevent cerebrovascular disease, more knowledge was clearly required about these risk factors, about the complications of thrombosis, and especially about their relation to the development of cerebrovascular disease. Consequently, research has been directed to greater understanding of the etiology and pathogenesis of hypertension, diabetes, atherosclerosis, and thrombosis. The most pressing need a decade ago was for animal models for the development of chronic hypertension, arteriosclerosis, and cerebrovascular disease. In fact, without these models research was impeded. Recently, animal models have become available for the experimental study of arteriosclerosis, hypertension, and stroke. For example, a colony of stroke-prone rats has now been developed (*34*).

Progress in understanding the various disorders that constitute the cerebrovascular diseases was slow until the last decade. Advances in neuroscience have now led to the recognition of distinctive and specific clinical stroke syndromes. It is now possible, by such techniques as brain-imaging (*53, 54*), to diagnose accurately a stroke as either ischemic (due to arteriosclerosis and narrowing of a cerebral vessel) or hemorrhagic (due to rupture of a cerebral vessel) and to identify precisely the site of the pathology (*55*, p. 70). The criteria for this differential diagnosis of the type and site of the stroke episode were previously unavailable, and this hindered the development of appropriate methods for specific medical or surgical management (*56*, p. 6). The effective treatment of hypertension has clearly had a major impact on stroke incidence and mortality (*55*, pp. 16 and 22).

The management of the stroke victim was, until recently, largely limited to bed rest and supportive therapy prescribed on the basis of empirical evidence. Use of the new diagnostic criteria, however, has led to earlier recognition of morphological and physiological changes in nerve and vascular tissue of the brain (*56*, p. 23), and permitted a rational approach to prompt medical and surgical treatment of hemorrhagic stroke. On the basis of results from epidemiological studies of risk factors and from metabolic studies of patients before or during ischemic stroke, it has become possible to initiate intervention measures such as administration of anticoagulants and antiplatelet-aggregating agents or surgery to prevent stroke or minimize brain tissue damage as a result of stroke (*57, 58*).

Sequelae of Problems

Arrhythmias. Sudden cardiac death is due to cardiac rhythm instability, possibly promoted by autonomic nervous system stimulation, and is widely recognized as a major public health problem. The inability in the 1970's to identify potential victims and the lack of effective therapies had posed major obstacles in dealing with the problem. Recently, however, significant advances have been made in understanding the mechanisms of lethal arrhythmias and consequently in the identification of subjects at risk. These advances led to consideration of the role of long-term antiarrhythmic drug therapy in the prevention of sudden cardiac death. It is now known that 50 percent of the posthospital myocardial infarction deaths occur within 24 hours of the onset of new coronary symptomatology. Suspected arrhythmias account for 77 percent of these deaths and pump failures account for only 23 percent.

Research on arrhythmia has led to a better understanding of conduction disturbances. Although all the answers are not yet available, the results of several long-term studies and prolonged monitoring indicate that many conduction disturbances are less ominous than had previously been thought. New antiarrhythmic agents that are becoming available for clinical investigation offer considerable promise of being effective against ventricular rhythm disturbances.

Several major clinical trials of antiadrenergic drug therapy have been conducted, including studies of alprenolol, timolol, metoprolol, propranolol, and practolol (β-adrenergic receptor blockers) in the prevention of death of patients with postmyocardial infarction. Although these new agents may be effective, their role in the more commonly encountered arrhythmias and in the management of ischemic heart disease in general still remains to be defined. Drugs that block the β-adrenergic system have shown particular promise in this regard (*59*). The Beta-Blocker Heart Attack Trial (BHAT), the most recently completed randomized, double-blind, multicenter clinical trial of propranolol versus placebo in patients enrolled 5 to 21 days after the onset of an acute myocardial infarction, exemplifies this (*60*). The primary objective of BHAT was to determine whether long-term administration of β-adrenergic blocking agent would result in a significant reduction in total mortality over the follow-up period. Data reported as of October 1981 revealed a mortality of 9.5 percent in the placebo group (183 deaths) and 7.0 percent in the proprano-

lol group (135 deaths), a reduction of 26 percent (*26*). The BHAT results indicate that the beneficial effects of a β-adrenergic blocking drug appear to occur primarily in the first year to 18 months following a myocardial infarction.

Major improvements have been made in computer-based rhythm analysis systems, thus facilitating clinical studies of arrhythmias and their treatment. Clinical trials to assess new antiarrhythmic drugs that may have more specific antiarrhythmic activity and greater efficacy in the control of arrhythmias are continuing. Attempts are also being made to determine whether changes in ion exchange and metabolism at the cellular level may explain both the cause and consequence of arrhythmias.

Heart failure and shock. It was postulated in the past that the amount of heart muscle that would be damaged irreversibly in the course of a heart attack was generally not fixed at the onset of the attack. It was believed that significant areas of the heart muscle were deprived of adequate blood flow and were in jeopardy but did not undergo instantaneous irreversible damage. One of the needs was to test this hypothesis and develop a means for minimizing damage to the jeopardized but not yet irreversibly damaged heart muscle. As a corollary, it was necessary to develop methods for quantifying adequately the extent of heart muscle that has undergone irreversible damage and for identifying for treatment the area that was potentially salvageable.

Several advances have been made in this area. The ability to reduce damage to heart muscles after heart attack has been improved by a variety of means (*49*). For example, animal studies have revealed various pharmacological agents that diminish the work load of the heart, improve blood flow and enhance the perfusion of ischemic areas, diminish swelling (thereby enhancing perfusion), and provide essential substrates. Several new techniques have been brought into limited clinical use, although most are still at the investigational stage. Furthermore, it remains to be demonstrated that immediate salvage of threatened myocardium is beneficial. Trials are under way to evaluate the 6-month efficacy of muscle salvage in terms of rhythm control, new infarction, and angina. Intra-aortic balloon pumping, a form of mechanical circulatory assistance, has been studied as a means of protecting the myocardium, but is more commonly used as part of the therapy for cardiogenic shock.

Techniques have been developed for assessing, with increasing precision, the amount of heart muscle undergoing damage. Such techniques include: sequentially mapping the electrical signals from the heart at various sites over the chest; measuring the amount of enzymes released by damaged heart muscle into the blood; identifying normal or damaged myocardium by radioisotopes; and measuring the extent and time of the movement of various portions of the heart by means of x-rays, echocardiograms, or radioisotopes (*49, 61, 62*). These techniques will allow more effective evaluation of new therapeutic agents in the future.

Circulatory assistance and diagnostic technology. The intra-aortic balloon was introduced over a decade ago, at first only as a short-term attempt to reverse shock in patients unresponsive to other forms of therapy. Efforts were made to implant an artificial heart in left ventricular assist devices in animals. The studies were fraught with technical problems, however, including blood clotting, lack of long-term availability of the units, the size of the devices, heat generation, and infection at the site of the percutaneous lead.

Intra-aortic balloon pumping is now in relatively common use. Although by itself the technique does not save the lives of those with cardiogenic shock associated with myocardial infarction, in some cases it does permit diagnostic studies that otherwise could not be undertaken. Similarly, it is used in some patients who have marginal or inadequate function of the heart in the preoperative period of open heart surgery. Pneumatically driven left ventricular assist devices, which should be able to support the systematic circulation of a patient with a permanently damaged left ventricle, have passed extensive bench and animal testing and are now undergoing short-term testing in man. Toward the goal of long-term, implantable, left ventricular assist devices, major advances have been made in increments of engine efficiency and total system reliability, miniaturization of components, the development of mechanically actuated pumps, materials fabrication, and pump configurations to achieve greater blood compatibility. When two mechanical pumps are used to replace natural ventricles and support pulmonary and systematic circulation, the device may be called an artificial heart. Such devices have functioned in animals (calves) for periods of 8 months to 1 year. Most recently, short-term ventricular assist pumps have been used to support circulation of patients who could not be removed from cardiopulmonary bypass machines following open heart surgery. After 7 days of pump assistance, some of these patients survived for well over a year (*63*).

For the most critically ill heart patient, human cardiac transplantation became a reality in 1967. The low survival rates, however, dampened the initial expectations. Consequently, the past decade has seen a reduction in heart transplant programs to only six centers throughout the world. Substantial progress in this area of research, however, has been made in the remaining centers in the diagnosis and control of graft rejections and operating techniques. Recent postoperative survival time of 70 percent for 1 year and 50 percent for 5 years, as well as successful rehabilitation of many transplant patients, has given new justification for continuation of clinical heart transplantation as a therapeutic modality (*64*). It can only be lifesaving, however, for a limited number of individuals.

The Future

What do all these advances mean? In each of the ten areas of cardiovascular medicine that have been described, there have been great advances. Should cardiovascular experts, researchers, and physicians feel comfortable with the gains that have made over the last 10 years? Probably not.

Cardiovascular disease still accounts for 51.2 percent of all deaths. There is still a long way to go in order to eradicate cardiovascular disease. Advances have been made in diagnostic screening and monitoring and it is possible to replace and repair diseased blood vessels. The heart can be approached surgically. There are new concepts of coronary care and improved medical therapies for hypertension, coronary disease, and congenital disease. New methods of chemotherapy and antibiotics are now available to treat hypertension and rheumatic heart disease, and new drugs have been developed to relieve angina, coronary vessel spasm, and congestive heart failure. It is possible that there is no cardiovascular disorder so complicated that it does not have the potential to be fully understood and controlled.

Sudden cardiac death, however, is responsible for too many deaths. Palliation and repair are much too costly. Transplants are not the ultimate answer. Thus the question is, what price must be paid to eradicate cardiovascular diseases. It is clear that prevention is the major long-term goal. The message from the recent past is that atherosclerosis does not have to be considered a natural process of

aging. Atherosclerosis, or at least its cardiovascular sequelae, can be controlled.

A focus on prevention means educating the public and the health professionals alike on how to obtain information on risk factors or ways to change life-styles and habits and on means to promote behavioral change. The effectiveness of nutritional intervention in hypertension and arteriosclerosis control still must be validated. More innovative basic research must be supported to clarify the causes of atherosclerosis and hypertension.

Today, we can treat and control the sequelae of these processes. If the process itself can be understood and controlled, prevention will be possible. The advances that have occurred, and their association with declining cardiovascular mortality, are encouraging signs that indicate the research is going in the right direction. Future goals, however, must include incisive research on ethology and pathogenesis; controversial concepts and hypotheses must be validated; and the public and health professionals must be given more information. Only in this manner can we hope to continue our efforts to control cardiovascular disease.

References and Notes

1. National Center for Health Statistics, *Monthly Vital Statistics Report* [DHHS Pub. No. (PHS) 80-1120, September 1980], vol. 29, No. 6.
2. *Fifth Report of the Director of the National Heart, Lung, and Blood Institute* [DHEW Pub. No. (NIH) 78-1415, National Heart, Lung, and Blood Institute, Bethesda, Md., February 1978].
3. R. I. Levy, in *The Cecil Textbook of Medicine*, P. B. Beeson, W. McDermott, J. B. Wyngaarden, Eds. (Saunders, Philadelphia, ed. 16, in press).
4. ———, *Arteriosclerosis* **1**, 312 (1981).
5. *National Heart, Lung, and Blood Institute's Fact Book for Fiscal Year 1980* (NIH Pub. No. 81-2105, National Heart, Lung, and Blood Institute, Bethesda, Md., 1981).
6. *Eighth Report of the Director of the National Heart, Lung, and Blood Institute, March 1981* (Government Printing Office, Washington, D.C., in press).
7. M. Feinleib, paper presented at the International Epidemiological Association meeting, Edinburgh, Scotland, 24 to 28 August 1981.
8. *Arteriosclerosis, 1981. Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute*, vol. 1, *Summary, Conclusions, and Recommendations* (NIH Pub. No. 81-2034, National Heart, Lung, and Blood Institute, Bethesda, Md., 1981).
9. World Health Organization, *World Health Statistics Annual 1979* (World Health Organization, Geneva, 1972 through 1979).
10. National Center for Health Statistics, *Health, United States, 1978* [DHEW Pub. No. (PHS) 78-1232, Government Printing Office, Washington, D.C., 1978].
11. R. I. Levy, *Annu. Rev. Public Health* **2**, 49 (1981).
12. R. Havlik and M. Feinleib, Eds., *Proceedings on the Conference on the Decline in Coronary Heart Disease Mortality, October 24–25, 1978.* [DHEW Pub. No. (NIH) 79-1610, National Heart, Lung, and Blood Institute, Bethesda, Md. 1979].
13. R. I. Levy, *Circulation* **60**, 1555 (1979).
14. "Eleventh Bethesda Conference: Prevention of Coronary Heart Disease, September 27–28, 1980," *Am. J. Cardiol.* **47** (No. 3), 713 (March 1981).
15. R. I. Levy, *Circulation* **65**, 217 (1982).
16. National Center for Health Statistics, *Advance Data from Vital and Health Statistics of the National Center for Health Statistics* [DHEW Pub. No. (PHS) 80-1250, Government Printing Office, Washington, D.C., 1980].
17. Office of the Assistant Secretary for Health, Office on Smoking and Health, *Smoking and Health: A Report of the Surgeon General* [DHEW Pub. No. (PHS) 79-5006, Government Printing Office, Washington, D.C., 1979].
18. *The Perrier Study: Fitness in America* (Louis Harris and Associates, Inc., for Perrier, New York, 1979).
19. *Health Maintenance* (Louis Harris and Associates, Inc., for Pacific Mutual Life Insurance Co., Newport Beach, Calif., 1978).
20. Atherosclerosis is a multifocal, multifactorial process involving the inner layer of an artery with the intracellular deposition of fat, particularly cholesterol ester, and an increase in arterial intimal cellularity, eventually culminating in extracellular cholesterol ester crystal, much fibrous tissue, and scarred and thickened plaques.
21. *Arteriosclerosis. The Report of the 1977 Working Group to Review the 1971 Report of the National Heart and Lung Institute Task Force on Arteriosclerosis*, [DHEW Pub. No. (NIH) 78-1526, National Heart, Lung, and Blood Institute, Bethesda, Md., 1978].
22. R. I. Levy and M. Feinleib, in *Heart Disease*, E. Braunwald, Ed. (Saunders, Philadelphia, 1980), pp. 1246–1278.
23. D. Velican and C. Velican, *Atherosclerosis* **38**, 39 (1981).
24. ———, *ibid.* **36**, 449 (1980).
25. R. Ross, *Arteriosclerosis* **1**, 293 (1981).
26. *Am. Heart Assoc. Monogr. No. 73*, published as *Circulation Suppl.* **62**, part 2 (November 1980).
27. D. D. Bradley, J. Wingred, D. B. Petitti, R. M. Krauss, S. Ramcharan, *N. Engl. J. Med.* **299**, 17 (1978).
28. R. I. Levy and B. M. Rifkind, *Circulation* **62** (part 4), 4 (1980).
29. J. R. A. Mitchell, *Br. Med. J.* **282**, 590 (1981).
30. G. Bergman, L. Atkinson, P. J. Richardson, K. Daly, M. Rothman, G. Jackson, D. E. Jewitt, *Lancet* **1981-I**, 569 (1981).
31. R. M. Robertson, D. Robertson, L. J. Roberts, R. L. Maas, G. A. Fitzgerald, G. C. Friesinger, J. A. Oates, *N. Engl. J. Med.* **304**, 998 (1981).
32. W. Friedewald, *Am. Heart Assoc. Monogr. No. 74*, published as *Circulation Suppl.* **62**, part 2 (No. 6) (December 1980).
33. J. J. Berger and B. L. Zaret, *N. Engl. J. Med.* **305**, 799 (1981).
34. *Report of the Hypertension Task Force*, vol. 1, *General Summary and Recommendations*, (NIH Pub. No. 79-1623, National Heart, Lung, and Blood Institute, Bethesda, Md., September 1979).
35. G. Onesti, M. Fernandes, K. E. Kim, Eds., *Regulation of Blood Pressure by the Central Nervous System* (Grune & Stratton, New York, 1976).
36. J. E. Sealey, S. A. Atlas, J. M. Laragh, *Am. J. Med.* **65**, 994 (1978).
37. A. B. Atkinson and J. I. S. Robertson, *Lancet* **1979-I**, 836 (1979).
38. Veterans Administration Cooperative Study Group on Antihypertensive Agents, *J. Am. Med. Assoc.* **213**, 1143 (1970).
39. Hypertension Detection and Follow-up Program Cooperative Group, *ibid.* **242**, 2562 (1979).
40. ———, *ibid.*, p. 2572.
41. A. S. Nadas, *N. Engl. J. Med.* **305**, 97 (1981).
42. *Workshop on Cardiomyopathies, July 11–12, 1978, Bethesda, Maryland* (NIH Pub. No. 79-1608, National Heart, Lung, and Blood Institute, Bethesda, Md., June 1979).
43. H. J. Berger and B. L. Zaret, *N. Engl. J. Med.* **305**, 855 (1981).
44. M. M. Bodenheimer, V. S. Banka, R. H. Helfant, *Am. J. Cardiol.* **45**, 674 (1980).
45. M. F. Victor, M. J. Likoff, G. S. Mintz, W. Likoff, *ibid.* **47**, 228 (1981).
46. *Am. Heart Assoc. Monogr. No. 79*, published as *Circulation Suppl.* **63**, part 2 (June 1981).
47. *Proceedings of the Workshop on Percutaneous Transluminal Coronary Angioplasty, June 15–16, 1979, Bethesda, Maryland* (NIH Pub. No. 80-2030, National Heart, Lung and Blood Institute, Bethesda, Md., March 1980).
48. K. M. Kent, R. O. Bonow, D. R. Rosing, C. J. Ewels, L. C. Lipson, C. L. McIntosh, S. Bacharach, M. Green, S. E. Epstein, *N. Engl. J. Med.* **306**, 441 (1982).
49. R. Rude, J. Muller, E. Braunwald, *Ann. Intern. Med.* **95**, 736 (1981).
50. M. S. Eisenberg, L. Bergner, A. Hallstrom, *Lancet* **1980-I**, 812 (1980).
51. E. M. Antman, P. H. Stone, J. E. Muller, E. Braunwald, *Ann. Intern. Med.* **93**, 875 (1980).
52. A. G. Turpie and J. Hirsch, *Crit. Rev. Clin. Lab. Sci.* **10** (No. 3), 247 (1979).
53. J. K. Campbell, O. W. Houser, J. C. Stevens, *Radiology* **126**, 695 (1978).
54. W. R. Kinkel and L. Jacobs, *Neurology* **26**, 924 (1976).
55. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, *Fundamentals of Stroke Care* [DHEW Pub. No. (HRA) 76-14016, Government Printing Office, Washington, D.C., 1976].
56. *Report of the Panel on Stroke, Trauma, Regeneration, and Neoplasms* [DHEW Pub. No. (NIH) 79-1915, National Institutes of Health, Bethesda, Md., 1979].
57. P. Didisheim, F. J. Kazmier, V. Fuster, *Thromb. Diath. Haemorrah.* **32**, 21 (1974).
58. T. M. Sundt, Jr., R. G. Siekert, D. G. Piepgras, *Mayo Clin. Proc.* **51**, 677 (1976).
59. Norwegian Multicenter Study Group, *N. Engl. J. Med.* **304**, 801 (1981).
60. Beta-Blocker Heart Attack Study Group, *J. Am. Med. Assoc.* **246**, 2073 (1981).
61. W. Bleifeld, D. Mathey, P. Hanrath, G. Buss, S. Effert, *Circulation* **55**, 303 (1977).
62. J. E. Muller, P. R. Maroko, E. Braunwald, *Ann. Intern. Med.* **82**, 516 (1975).
63. W. S. Pierce, G. V. S. Parr, J. L. Myers, W. E. Pae, Jr. A. P. Bull, J. Waldhausen, *N. Engl. J. Med.* **305**, 1606 (1981).
64. R. B. Griepp, *Transplant Proc.* **11**, 285 (1979).
65. National Center for Health Statistics, *Vital Statistics Rates in the United States, 1900, 1960* (PHS Pub. No. 1677, Government Printing Office, Washington, D.C. 1960).
66. ———, *Monthly Vital Statistics Report* **22**, No. 11 (1974).
67. ———, *ibid.* **29**, No. 13 (1981).

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