INTRODUCTION

Knowledge of the determinants, distribution, and sequelae of coronary heart disease (CHD) in populations of the world's developed nations is extensive, is growing rapidly, and extends from the molecular level of individual persons to total societies. Lifestyle changes as well as public health and medical care advances in the prevention and treatment of CHD from the 1950s to the 1980s were accompanied by a 50 percent decline in CHD mortality in countries such as the United States (1). CHD nevertheless remains the leading cause of death in developed nations and is predicted to achieve that status worldwide within decades (2).

The clinical manifestations, morbidity, and mortality of CHD are end-stage events triggered after decades of progression of asymptomatic, subclinical coronary atherosclerosis. The determinants of both the subclinical and clinical stages of the disease are numerous and varied, including risk factors for individual persons, group characteristics of entire populations, and environmental exposures. Broad, multilevel categories of CHD determinants and their interrelations are illustrated in figure 1. In this conceptualization, the determinants are categorized as follows: inherited genes and culture; biomedical, lifestyle, and psychosocial risk factors at the individual level; social, political, and economic factors at the group and aggregate levels; and social, medical care, physicochemical, and biologic exposures at the environmental level. Each interactively influences population levels of and trends in CHD over time. CHD susceptibility is transmitted intergenerationally, is conditioned environmentally, evolves and is manifest clinically over the time scale of each individual person's life, and is expressed in population rates of CHD during societies' histories.

In this paper, no attempt is made to detail the wealth of current information on the CHD determinants in each category shown in figure 1; rather, a brief overview of the contemporary status of general knowledge at each level is presented and is illustrated with selected examples. Based on this synopsis, the prospects for CHD epidemiology in the 21st century within and across these spatial and temporal biosocial levels are addressed.

ACUTE ISCHEMIC EPISODES AND THEIR CLINICAL EPIDEMIOLOGY

The incidence of angina, acute myocardial infarction, and sudden death, the major clinical manifestations of CHD assessed epidemiologically, varies according to risk factors, age, gender, and ethnicity at the individual level and among countries, regions, and social strata within countries at the population level, and it has varied markedly over time (3). Unstable angina, acute myocardial infarction, and acute ischemic episodes result from sudden, life-threatening, impaired blood supply to the myocardium and are usually precipitated by lumen-obstructing thrombi that are superimposed on lipid-rich coronary artery plaques after they rupture (4). Until recently, the "natural history" of coronary atherosclerosis at these advanced stages of the disease was resistant to therapeutic intervention; it now can be converted to a favorable clinical course modifiable by medical intervention, which is the subject matter of clinical CHD epidemiology and its clinical trials (5). Often, infarctions can be aborted, their extension and severity reduced, and progression from unstable angina to myocardial infarction prevented, given prompt medical intervention. In-hospital case fatality rates have declined (6), initially in parallel with the development of coronary care units and subsequently with the development of medical and surgical techniques for thrombolysis and coronary artery revascularization. Advances in diagnosis and treatment, both in and out of hospital, have contributed to the decline in CHD mortality, but how much of the improved in-hospital prognosis is attributable to treat-
ment, admission of less severe cases, or more favorable risk factor profiles of cases is unclear (7–9).

There has been differential use of diagnostic, medical, and surgical procedures such as angiography, thrombolytic therapy, and coronary artery bypass surgery in relation to ethnicity, socioeconomic status, and gender; these procedures are used less frequently for women and in minority and socioeconomically disadvantaged strata of the US population (10). Additionally, use of simple adjunctive medication such as aspirin and beta blockers of proven efficacy in clinical trials, during and after acute ischemic episodes, varies across regions of the United States (11). Furthermore, there are complex interactive associations of CHD severity, treatment, and prognosis with supraindividual group and population characteristics.

Improved in-hospital survival of acute ischemic episodes can be expected to increase the prevalence in populations of persons more susceptible to recurrent episodes and chronic cardiovascular disease complications such as congestive heart failure. Regardless of extent, reduced hospital mortality cannot prevent most CHD deaths, since the majority (approximately 60 percent of all deaths attributed to CHD) occur out of hospital. It is difficult to obtain valid estimates of the levels of and trends in sudden CHD deaths in and out of hospital; however, available US data indicate increasing inequalities in relation to the socioeconomic status of persons and the social environment of populations (12). Thus, organization and use of the medical care system, which offers preventive and therapeutic treatments in and out of hospital, is becoming an increasingly important environmental determinant of the distribution of CHD in populations.

**SUBCLINICAL ATHEROSCLEROSIS**

Despite its marked increase with age, and in contrast to earlier beliefs, atherosclerosis resulting in CHD is not a degenerative, inevitable consequence of aging. Atherosclerosis begins early in life, and it results from endothelium injury and repair as well as from active subintimal inflammatory, immunologic, metabolic, and hemostatic processes involving multiple systems and cell types (13). It progresses in stages from deposition of lipid-laden macrophages (foam cells) to fatty streaks and fibrous plaques with lipid core and calcium deposits; complicated lesions result from endothelium disruption, hemorrhage, and occlusive thrombosis (14, 15). Autopsy studies disclose geographic variation in atherosclerosis prevalence and severity associated with population mortality rates and association of atherosclerosis with the established risk factors, even at young ages (16). Many of the pathologic cellular, histologic, gross structural, and functional changes in arteries can now be assessed in population studies by measuring circulating markers of cell biology processes and by using noninvasive imaging and functional techniques.

Results of ultrasound imaging of superficial arteries, such as the carotids, presently serve as a marker of sys-
temic atherosclerosis. Carotid intima-media wall thickness provides reliable and valid estimates of the presence and extent of local atherosclerosis, is correlated with angiographic coronary atherosclerosis, is related to the established risk factors, and predicts prevalent and incident CHD (17, 18). Thickness of this wall also varies strongly and inversely with socioeconomic status (19). Indices of atherosclerosis in the arterial beds supplying the lower extremities are obtained from the ratio of ankle to brachial artery blood pressure. This index also is related to the established CHD risk factors and to prevalent CHD (20). More direct epidemiologic assessment of the coronary arteries may be provided by quantitative radiologic estimation of calcium deposition. Coronary calcium scores predict the extent of angiographic disease and CHD case prognosis and are correlated with established risk factor levels (21); research currently is under way to evaluate their predictive utility in large population studies. New imaging, functional, and marker tests move epidemiologic studies of atherosclerosis to earlier stages, enable testing of mechanisms at multiple levels, and are applicable over the life course of persons in populations.

RISK FACTORS

Risk factors are central to CHD epidemiology. The term risk factor is used here to denote attributes of persons that are predictive of incident CHD with evidence of probable causality; in contrast, the term risk indicator denotes a statistical predictor whose causal role is uncertain (more than 200 have been identified). Risk factors include biomedical, behavioral, and lifestyle characteristics. Those firmly established, for example, include serum total and low density lipoprotein cholesterol, blood pressure, smoking, diabetes, and diet, are supported by results of numerous observational epidemiologic and genetic, clinical, and pathophysiologic investigations and animal experiments (22, 23). Clinical trials of serum total and low density lipoprotein cholesterol lowering, which reduced occurrence of clinical events and progression of atherosclerosis by approximately 30%, are under way to evaluate their predictive utility in large population studies. New imaging, functional, and marker tests move epidemiologic studies of atherosclerosis to earlier stages, enable testing of mechanisms at multiple levels, and are applicable over the life course of persons in populations.

Risk summary scores based on the established risk factors in one population rank order CHD risk for persons in other populations with different CHD rates, but they usually do not predict absolute incidence rates across socially diverse populations. The aggregate level of established major risk factors for persons does not completely explain differences in CHD mortality levels even among developed nations (31). When differences among socially defined subpopulations are explained statistically, inclusion of additional factors—such as dietary components and physical activity at the behavior level; hostility and anger at the psychological level; indices of obesity and body fat distribution at the anthropometric level; serum fibrinogen at the hemostatic level; and serum high density lipoprotein cholesterol, lipoprotein(a), triglycerides, insulin, and homocysteine at the metabolic and biochemical levels—improves quantitative predictiveness more than is achieved by considering the major established risk factors only (32).

A large number of studies have reported on the association of certain chronic bacterial and viral infections with atherosclerosis and clinical manifestations of CHD, although causality remains uncertain (33). The etiologic role of organisms such as *Chlamydia pneumoniae* may be clarified by the results of clinical trials of ongoing antibiotic treatment for secondary prevention of CHD (34). Among the emerging risk factors, markers of inflammation and acute-phase reactants, circulating cytokines, C-reactive protein, white blood cell count, serum albumin, and fibrinogen are predictors of incident CHD and recurrent acute myocardial infarction, but it is presently uncertain whether they reflect the consequences or the causes of atherosclerosis and its clinical sequelae (35, 36).

INHERITANCE OF CHD SUSCEPTIBILITY

Family history of CHD is associated with each of the following stages in the development of the disease in probands: risk factor elevation (37), subclinical atherosclerosis (38), and clinically manifest CHD (39). Aggregation of the major risk factors present in fami-
lies does not totally account for the within-family aggregation of CHD. Furthermore, occurrence of CHD in families usually does not follow the pattern of simple Mendelian inheritance, leading to the aphorism that CHD aggregates but does not segregate within families. Inheritance of increased susceptibility to CHD results from the intergenerational transmission of cultural, lifestyle, and shared environmental determinants of CHD (40) as well as multiple susceptibility genes. Parental socioeconomic status is a strong determinant of the adult socioeconomic status of offspring, and CHD-relevant lifestyle, behavioral, dietary, and smoking practices may thereby aggregate within families and be expressed as adult CHD risk (41, 42).

A large number of genes associated with increased risk of CHD have been identified, generally by their relation to the known risk factors. For example, numerous biochemical steps in the metabolism of serum lipids (43) and physiologic steps in the regulation of blood pressure (44) are known to be influenced by genes and therefore influence CHD risk. Thus, although a few genetic disorders of large, single gene effects exist, such as familial hypercholesterolemia, CHD and its major risk factors generally involve many genes, each having a relatively small effect. Regarding lipids, for example, lipoprotein receptors, apolipoproteins and lipases, and structural and functional gene product proteins have been identified as influencing each of the large number of biochemical steps involved in absorption of dietary fatty acids and cholesterol and in synthesis, transport, and metabolism of serum lipoproteins. Numerous mutant alleles have been found for genes identified to date. Given the large number of susceptibility genes and their mutant alleles, each responsible for only a small effect, and the general modification of genes' effects in different environments and in the presence of other genes, CHD is classified as a complex genetic disorder. Gene-by-environment and gene-by-gene interactions invalidate meaningful attempts to estimate the relative importance of genes versus environment or the independent effect of a single gene or single risk factor under all circumstances.

Multiple interdependent steps are involved in maintenance of physiologic and biochemical homeostasis of levels of the risk factors and mediators. Although each step is influenced by the genotype, mapping of the susceptibility genotypes to risk factor levels and to subclinical and clinical CHD phenotypes, modified as they are by internal and external environments, presents formidable theoretical and methodological challenges (45).

**BEHAVIORAL, PSYCHOSOCIAL, AND SOCIAL ENVIRONMENTAL DETERMINANTS**

Studies reporting the association of psychosocial factors, such as hostility, depression, low social support, social isolation, job instability, and powerlessness, with CHD have variously been summarized as inadequate, conflicting, or inconclusive for women (46) and conversely as strong enough to enable clinical trials to be undertaken of the efficacy of modifying some of these factors (47, 48). In contrast, strong, consistent evidence exists of the association of CHD risk behavior, risk factors, subclinical atherosclerosis, and clinically manifest CHD with individual socioeconomic status (49). Levels of and long-term trends in CHD also vary according to the social environmental characteristics of nations and of geopolitical units within nations (50). CHD mortality rates increased during the transition of rural, agrarian, and economically underdeveloped societies to urbanized, industrialized, and modernized societies. Socioeconomic status was related positively to CHD during the ascending limb of the epidemic; currently, during the descending limb of the epidemic in countries such as the United States and Great Britain, socioeconomic status at the individual and societal level is becoming increasingly inversely associated with CHD (51).

The quantity of knowledge about CHD determinants, ability to change behavior, availability of preventive and therapeutic resources, salience of health compared with other concerns, and preventive and therapeutic resources in communities of residence is greater as socioeconomic status increases. All stages in the development of CHD over the life course—that is, CHD-relevant knowledge, attitudes, and beliefs; risk behaviors; biomedical risk factors; preventive medical care; subclinical atherosclerosis; clinical incidence; therapeutic medical care; prevalence; secondary preventive medical care; prognosis; and mortality—are related to social organization and social exposures (52).

The social characteristics of geopolitically defined regions, for example, levels of income, education, and types of occupations, are related at the aggregate level to their residents' CHD mortality rates (53). Additionally, and conceptually distinct, measures of the distribution per se of these attributes within populations may be related to CHD. Income inequality, a characteristic of the population and not the individual person, as the unit of study reportedly is associated with CHD mortality across nations and among states in the United States (54).

**CHD EPIDEMIOLOGY IN THE NEAR FUTURE**

Given the global increase in life expectancy and the greater risk of CHD with increasing age, worldwide increases in CHD are predictable, with CHD as the leading single cause of death. However, limitations in long-term forecasting of population levels of and
trends in CHD is illustrated by the failure to predict, or even in retrospect to explain adequately, the onset of the decline of CHD mortality rates in the United States and most western industrialized nations in the 1960s. To date, controversy remains regarding the relative contribution of decreasing incidence and decreasing case fatality to the subsequent decline in CHD mortality in these countries (55, 56). The failure to predict trends in CHD risk-related factors also is illustrated by the unanticipated current worldwide increase in obesity. In addition, mortality differences are widening among ethnic and socioeconomic groups in the United States, and recent trend analyses suggest flattening of the CHD decline for the aggregate population despite increasing epidemiologic knowledge, educational programs, and public health and medical care efforts. Similar uncertainty exists about the causes of the presently high and rising rates of CHD in nonmarket-economy, industrialized countries of eastern Europe. Cohort studies in these settings indicate they are only partially explained by elevated levels of some of the established risk factors, such as hypertension and smoking (57).

CHD rates appear to be rising in developing nations (58), although comprehensive and valid epidemiologic data in these settings are scarce. Prediction of future patterns of CHD epidemics for these nations can be based on earlier experiences of now-developed nations. For example, a decrease in the burden of infectious diseases and undernutrition can be expected, with an increase in life expectancy and the numbers of older persons. The transition from poor, predominantly rural agrarian, hard-manual-labor societies with stable, traditional cultural and social values to more affluent, urbanized, industrialized societies with minimal physical activity demands, diets rich in calories and saturated fats, increased smoking, and new psychosocial stresses will prime their populations for the development of atherosclerosis throughout life and for the emergence of clinical CHD sequelae in large numbers of persons at older ages. Thus, despite increases in biomedical knowledge about CHD, the disease can be expected to increase in frequency and importance worldwide as a consequence of changes in population composition and societal organization and of technologic advances.

In the early 21st century, as a simple extrapolation of ongoing trends, one can confidently predict a marked increase in knowledge at each of the CHD epidemiology levels shown in figure 1 and described in this paper. Typing of the entire genome plus indices derived from presently established and emerging risk factors—simply, reliably, validly, and inexpensively measurable many times over the life course—will make it possible to characterize and identify high-risk persons earlier in life. Modifying a person’s CHD risk with lifestyle interventions and medical treatments will be more efficacious and potentially more effective. Continuing advances in treatment of ischemic episodes will result in increasing survival and decreased morbidity but with consequent increases in prevalence of the disease. Study of the emerging risk factors will increase knowledge about mechanisms responsible for atherosclerosis and its clinical complications. Technologic innovations, which permit noninvasive assessment of the structure and function of the coronary arteries and heart in population studies, combined with methodological and analytical advances in information processing, will enable extended epidemiologic investigations of all stages from clinical CHD and subclinical coronary atherosclerosis to risk factors and their determinants beginning early and continuing over a person’s life.

Despite the present and predicted future expanding wealth of epidemiologic and biomedical knowledge about the determinants of the disease in persons within populations, the increasing worldwide epidemic of CHD presents an urgent public health challenge. A shift in the distribution of the established risk factors to lower values for populations with currently high levels of CHD would greatly reduce the public health burden of this disease. Evidence indicates that primordial prevention, that is, preventing populations from developing deleterious levels and distributions of the established coronary risk factors, would remove CHD as the leading cause of death. This goal will be achieved with increasing recognition of the different theoretical and methodological requirements for epidemiologic studies at different levels of biosocial organization; epidemiology will focus on populations and their attributes as the units of study in addition to the study of persons within populations (59). The challenge will be to integrate studies of characteristics of individual persons with those of their social organizations and environments, providing perspectives that explain the epidemiology of CHD both within and among populations, thereby enabling the epidemic to be controlled further and eventually eradicated.

ACKNOWLEDGMENTS

The author thanks Dr. Gerardo Heiss for critical review of the manuscript and Marilyn Knowles for preparing the figure.

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