Epidemiology of Coronary Heart Disease: The Framingham Study

W. P. CASTELLI, M.D.
Framingham, Massachusetts

Coronary heart disease continues to be the number one cause of death in most Northern European, North American and other industrialized Caucasian societies. By the age of 60, every fifth man and one in 17 women have some form of this disease. One in 15 men and women will eventually have a stroke. Other cardiovascular diseases related to atherosclerosis are also important. Epidemiologic (prospective) studies enable one to predict most of the potential victims of cardiovascular disease, years before they become ill. An increase in total to high-density lipoprotein cholesterol ratio, hypertension, cigarette smoking, excess weight, elevated blood sugar levels, lack of exercise, stress, electrocardiographic abnormalities, and other factors are associated with the development of these diseases. Intervention trials have generally shown that lowering "risk factors" reduces the subsequent rate of coronary heart disease, stroke, and other cardiovascular disease. Most highly susceptible subjects have problems with several risk factors. Management of one should not interfere with management of another if optimal health is sought.

The association of many antecedent factors with various cardiovascular endpoints such as coronary heart disease, atherothrombotic brain infarction, and peripheral vascular disease continues to be illuminated by prospective ongoing studies of cardiovascular epidemiology.

The purpose of this report is to update newer aspects of the "risk factor" approach in coronary heart disease and to comment on the implications of intervention on risk factors in an effort to alter the course of these pathologic processes in individual patients. Medicine has become so compartmentalized that we now have specialists working only on blood pressure, or blood cholesterol, or blood sugar, and the like. Sometimes one wonders if the right hand knows what the left hand is doing. One cannot ignore the impact of measures that may help in one area only to cause problems in another. The recent results of the Multiple Risk Factor Intervention Trial [1] illustrate that such problems are not just theoretic, but real; in the men receiving antihypertensive drugs the decrease in cholesterol was only half as much as that in the men not receiving such therapy. One can only guess at the extent to which this blunted the efficacy of the total intervention measures, but its implications should concern us all.

From the Framingham Heart Study, Framingham Massachusetts and the National Heart, Lung and Blood Institute. Requests for reprints should be addressed to Dr. W. P. Castelli, The Framingham Heart Study, 118 Lincoln Avenue, Framingham, Massachusetts 01701.

METHODS

Since 1949, 5,209 men and women aged 30 to 62 years who for the most part were randomly selected from 10,000 men and women living in Framingham, Massachusetts, have been followed biennially. Of these, 5,127 were free of all clinical evidence of cardiovascular disease at entry. Standardized

examinations included a complete history, physical examination, chest radiography, electrocardiogram, and various blood chemistry measures such as blood cholesterol (by the Abel-Kendall method) [2], triglycerides (after Lederer-Kessler) [3], high-density lipoprotein cholesterol (modification after Burstein et al) [4] and blood glucose (after Somogy) [5]. Briefly, the five coronary heart disease endpoints [6] were (1) angina pectoris defined as short duration chest discomfort as a result of exertion or excitement and relieved in five to 15 minutes by rest and confirmed by two separate physician interviewers; (2) coronary insufficiency defined as prolonged chest pain (greater than 15 minutes associated with transient nonspecific ST-T wave changes and normal blood enzymes; (3) myocardial infarction diagnosed as prolonged chest pain associated with appropriate Q wave changes and/or serum enzyme changes; (4) sudden death defined as having occurred within one hour in a person for whom there was no other explanation for death; and (5) non-sudden coronary heart disease death occurring after one hour in a person in whom an acute myocardial process was in progress. Standard statistical Student's t test, chi-square tests, multiple logistic function tests, and likelihood ratio tests were used to assess statistical significance [7,8]. The duration of follow-up in this paper is variable and ranges from four to 28 years depending on the factor in question.

RESULTS

Rate of Coronary Heart Disease. **Figure 1** shows the rate at which new cases of coronary heart disease occurred in the first 14 years of the study. For example, in every eighth man 40 to 44 years of age at entry and free of coronary heart disease, some form of coronary heart disease developed within 14 years. Comparable rates for other age groups were every sixth man aged 45 to 49 years of age, every fifth man aged 50 to 54, every fourth man 55 years of age or more. In younger women the rates ran much lower, particularly before menopause. Of the 1,600 premenopausal women in the study coronary heart disease developed in only 11 while they were still premenopausal. Once a woman passes the menopause, the incidence of coronary heart disease rises dramatically. By the age of 60 years, in every fifth man and every 17th woman some form of coronary heart disease has developed.

Blood Cholesterol and Other Lipids. In Framingham it was soon apparent that by the sixth year of follow-up the simple total cholesterol was powerfully related to the subsequent rate of coronary heart disease (**Figure 2**). The total cholesterol is the sum of cholesterol carried in chylomicrons, very low-density lipoproteins, intermediary-density lipoproteins, low-density lipoproteins, and high-density lipoproteins.

No quantitative scales are available for chylomicrons and intermediary-density lipoprotein cholesterol but less than 0.2 percent of the population have abnormalities in these areas. Low-density lipoprotein and very low-density lipoprotein show positive associations with

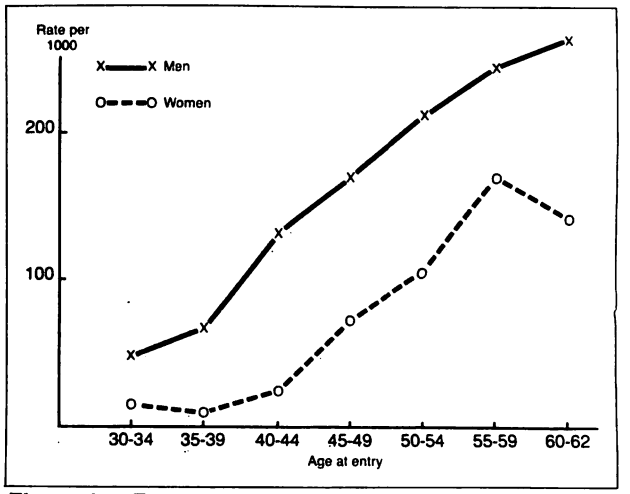

Figure 1. *Fourteen-year incidence of coronary heart disease (all clinical manifestations) according to age and sex.*

subsequent rates of coronary heart disease although on multivariate analysis only low-density lipoprotein retains an independent relationship to this disease with increasing age (**Figure 3**).

Very low-density lipoprotein was associated with risk in the younger men in the Framingham cohort but subsequently, over the age of 50, very low-density lipoprotein is not related to coronary heart disease. In women there is a powerful univariate association be-

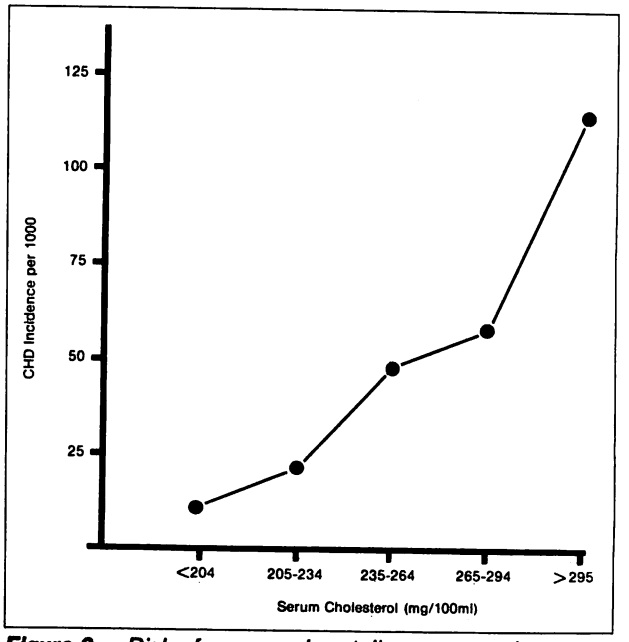

Figure 2. *Risk of coronary heart disease over six years in men aged 30 to 49 years, according to serum cholesterol levels.*

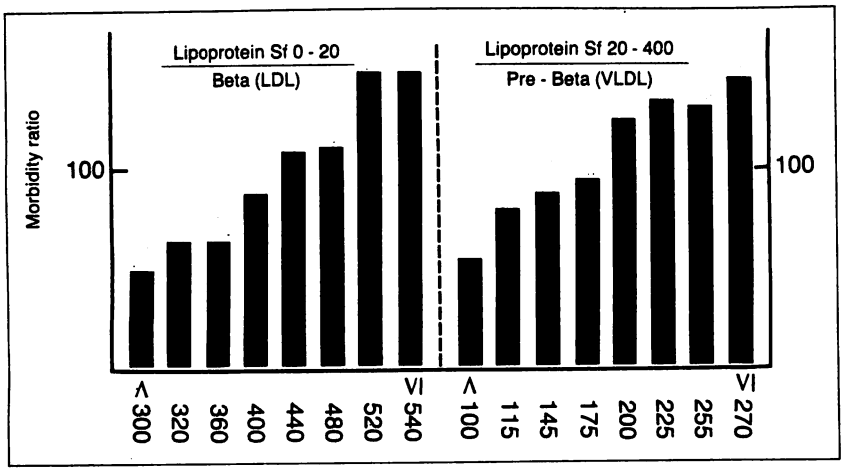

Figure 3. *Blood lipids and risk of coronary heart disease.*

tween coronary heart disease and very low-density lipoprotein at all ages, but this is no longer apparent after adjusting for other lipid fractions in older women (**Table I**). High-density lipoprotein is negatively associated with risk, the higher values running much lower rates of coronary heart disease; these relationships are independent on multivariate analysis (**Table II**). **Figure 4** shows that the overlap of cholesterol levels in subjects free of coronary heart disease versus those in whom coronary heart disease develops is great; therefore, the use of the total cholesterol in individual cases is fraught with uncertainty. Use of combinations of lipid measures as shown in **Table III** suggests that the ratio of total to high-density lipoprotein is as good as any other and represents a simple scale for the clinician to follow. **Table IV** gives us the relationship of total cholesterol:

TABLE I **Regression Coefficients on the Incidence of Coronary Heart Disease on Low-Density Lipoprotein and Very Low-Density Lipoprotein**

	Follow-Up (years)	Regression Coefficients			
		Univariate		Multivariate	
		Men	Women	Men	Women
Under age 50					
LDL-C (sf 0–20)	18	0.262	0.451†	0.233*	0.376*
VLDL-C (sf 20–400)	18	0.294*	0.268*	0.204*	0.215*
Over age 50					
LDL cholesterol	4	0.210*	0.254*	0.251*	0.189
VLDL-C (fasting triglycerides)	4	0.075	0.312†	0.002	0.106

NOTE: Sf = Svedberg units (ultra centrifuge).
* $p < 0.05$.
† $p < 0.001$.

TABLE II **Incidence of Coronary Heart Disease by High-Density Lipoprotein Cholesterol Level, Framingham Study, Examination 11**

HDL Cholesterol Level (mg/ml)	Men			Women		
	CHD Incidence	Population at Risk	Rate/1,000	CHD Incidence	Population at Risk	Rate/1,000
All levels	79	1,025	77.1	63	1,445	43.6
<25	3	17	176.5	0	4	0.0
25–34	17	170	100.0	11	67	164.2
35–44	35	335	104.5	12	220	54.5
45–54	15	294	51.0	19	386	49.2
55–64	8	134	59.7	14	353	39.7
65–74	1	40	25.0	3	216	13.9
≥75+	0	35	0	4	199	20.1

HDL = high-density lipoprotein; CHD = coronary heart disease.

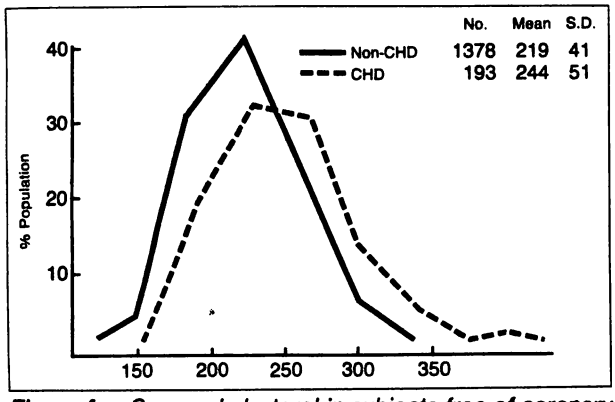

Figure 4. Serum cholesterol in subjects free of coronary heart disease versus those in whom coronary heart disease developed within 16 years.

high-density lipoprotein ratios to clinical subgroups. Choosing a single value is hazardous but produces a more practical clinical tool. Subjects whose ratio of total cholesterol: high-density lipoprotein exceeds 4.5 should be treated to lower this ratio to 4.5; half the women and two thirds of the men in the United States have ratios above 4.5.

Blood Pressure. There is a curvilinear relationship of blood pressure to subsequent development of coronary heart disease (**Figure 5**). Interestingly, either the systolic or the diastolic pressures could be used to predict risk. The dilemma is to decide at what blood pressure one should definitely intervene. Categorical values such as a systolic pressure of 160 mm Hg or greater or a diastolic pressure of 95 mm Hg or greater increase the risk of coronary heart disease two- to threefold; ather-

TABLE III Likelihood Ratios for Various Lipid Profiles of Coronary Heart Disease, Framingham Study, Examination 11

Lipid Profile	Men	Women
HDL cholesterol	14.03‡	21.21‡
LDL cholesterol	4.39*	4.53*
Triglyceride	0.51	9.52†
Total cholesterol	1.98	2.26
HDL cholesterol/total cholesterol	17.11‡	20.41‡
LDL and total cholesterol, triglyceride	8.26*	19.69‡
HDL and total cholesterol, triglyceride	19.19‡	24.21‡
HDL and LDL cholesterol, triglyceride	18.90‡	24.73‡
HDL and LDL cholesterol	18.66‡	23.70‡
HDL cholesterol/total cholesterol, LDL cholesterol	17.16‡	20.77‡

NOTE: This table estimates the relative power of a test or set of tests to predict coronary heart disease from asymptomatic subjects. The higher the number the better the ability of the test(s) to predict. HDL = high-density lipoprotein; LDL = low-density lipoprotein. * = $p < 0.05$; † = $p < 0.01$; ‡ = $p < 0.001$.

TABLE IV Selected Groups According to Increasing Average Level of Total Cholesterol to High-Denisty Lipoprotein Cholesterol (Levels of Low-Density Lipoprotein to High-Density Lipoprotein Cholesterol Are Given for Comparison)

Group	T-C:HDL-C	LDL-C:HDL-C
Vegetarians	2.9	1.7
Boston Marathon runners	3.5	2.0
Average among females without CHD	4.4	2.9
Average among males without CHD	5.1	3.3
Average among females with CHD	5.3	3.5
Average among males with CHD	5.8	3.8
Type IIA hyperlipidemia among females	6.0	4.5
Type IV hyperlipidemia among females	6.1	3.5
Type IV hyperlipidemia among males	6.9	3.8
Type IIA hyperlipidemia among males	7.3	5.5
Type IIB hyperlipidemia among males	7.3	5.2
Type IIB hyperlipidemia among females	8.4	6.0

T-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.

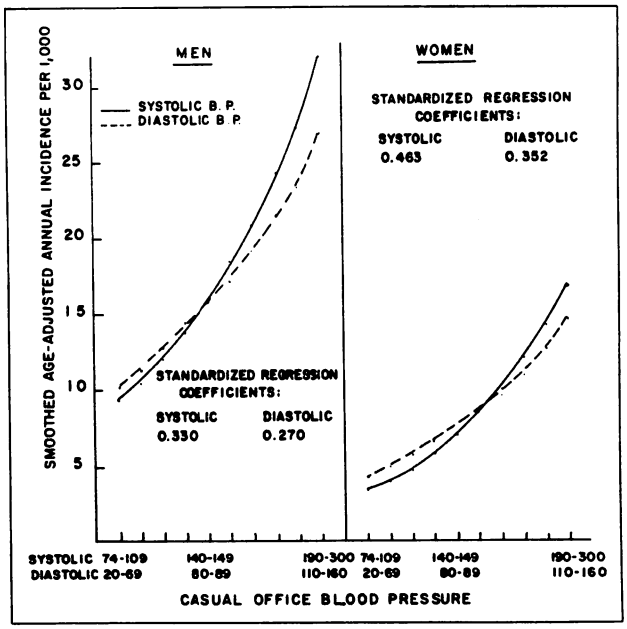

Figure 5. Incidence of coronary heart disease according to systolic versus diastolic blood pressure in men and women aged 45 to 74 years; Framingham study, 20-year follow-up.

TABLE V **Relative Odds for the Development of Overt Clinical Coronary Heart Disease for Various Electrocardiographic Abnormalities (14 years)**

	Men	Women
Nonspecific ST-T	1.66	1.92
Left ventricular hypertrophy by electrocardiogram	3.23	3.22
Atrial fibrillation	2.0	2.7
Right bundle branch block	2.0	3.1
Left bundle branch block	2.9	4.2

NOTE: All values statistically significant, at least $p < 0.05$.

othrombotic brain infarction is increased sevenfold at these levels. Borderline hypertension (systolic pressure 140 to 159 mm Hg, diastolic pressure 90 to 94 mm Hg) increase coronary heart disease rates by 50 percent; there is a threefold increase in stroke at these levels.

Electrocardiographic Abnormalities. Left ventricular hypertrophy, right and left bundle branch block, and nonspecific ST and T wave abnormalities on a resting electrocardiogram are all predictors of subsequent clinical coronary heart disease, particularly the death endpoints. Left ventricular hypertrophy by electrocardiogram is an especially dangerous finding on an electrocardiogram. Atrial fibrillation increases by twofold the risk of death. **Table V** summarizes the relative risks of overt coronary heart disease by various electrocardiographic abnormalities.

Blood Glucose. The effect of whole blood nonfasting glucose levels is shown in **Figure 6.** There is a modest increase in risk even at blood glucose levels within the usual range of values, but the dramatic increase in risk is at the higher glucose levels experienced by the major proportion of the patients with diabetes mellitus. These relationships are statistically independent on multivariate analysis in the women but not in the men.

Weight. Figure 7 shows that weight is a powerful predictor of virtually all cardiovascular endpoints in men and women, and such relationships for coronary heart disease are independent in men after eight years of follow-up and in women after 14 years of follow-up on multivariate analysis (**Table VI**). The relationship to death appears to be U-shaped and as such prompted some health professionals to recommend higher weights. The deaths at the lower weights are cancer deaths, whereas those at the higher weights are predominantly cardiovascular deaths. Cigarette smoking appears to be the major implicating factor as seen in **Figure 8,** suggesting that it is dangerous to be skinny if you smoke but a health attribute if you do not!

Exercise. Those people who stay more physically active have in general fared better in Framingham for virtually every manifestation of coronary heart disease (**Figure 9**). At the time few of this cohort indulged in jogging or running, and such activities will have to be judged in the second generation currently under study.

Smoking. Cigarette smokers and other smokers who inhale, but not the traditional non-inhaling cigar and pipe smoker, run about one and a half times the rate of people who do not smoke. If you stop smoking for one year in Framingham, the risk falls back to the rate of people who never smoked (**Figure 10**). If you switch to a filter cigarette the rate is, if anything, worse (**Figure 11**). Subjects are particularly prone to sudden death if they smoke.

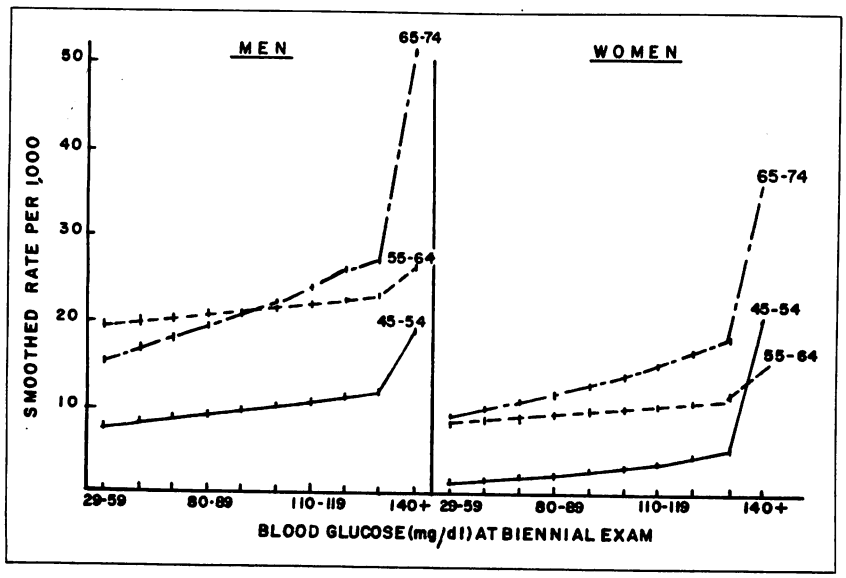

Figure 6. *Average annual incidence of coronary heart disease according to blood glucose level. Sixteen-year follow-up, men and women 45 to 74 years of age, Framingham study. Source: monograph section no. 26, Table I-6-B, National Institutes of Health.*

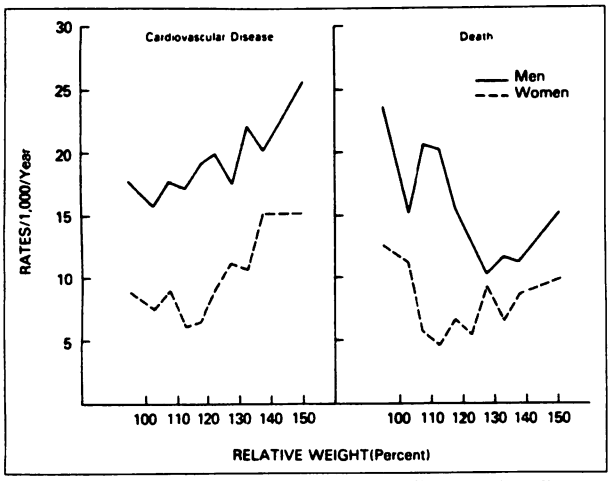

Figure 7. Two-year incidence of cardiovascular disease and death by relative weight. Framingham study: 18-year follow-up. Data shown are crude rates for the age group 45 to 74.

Stress. Framingham Type A personality, characterized by need to excel, bossiness, time urgency, eating quickly, impatience and job uncertainty coupled with a workaholic nature, is associated with almost a doubling of risk in men and women (**Figure 12**). However, in the men this finding was restricted only to the white collar workers; it was not found in blue collar workers. In women the relationship was the same in working women and housewives.

Family History. Persons whose father died prior to age 60 have double the rate of coronary heart disease; persons whose parents died later are at standard risk. A family history of hypercholesterolemia means the person has a 50 to 50 chance of becoming hypercholesterolemic, which triples the rate of coronary heart disease prior to age 60.

Estrogen. Recently, in a small case-control study, we found that men in whom a myocardial infarction developed had significantly higher estradiol levels.

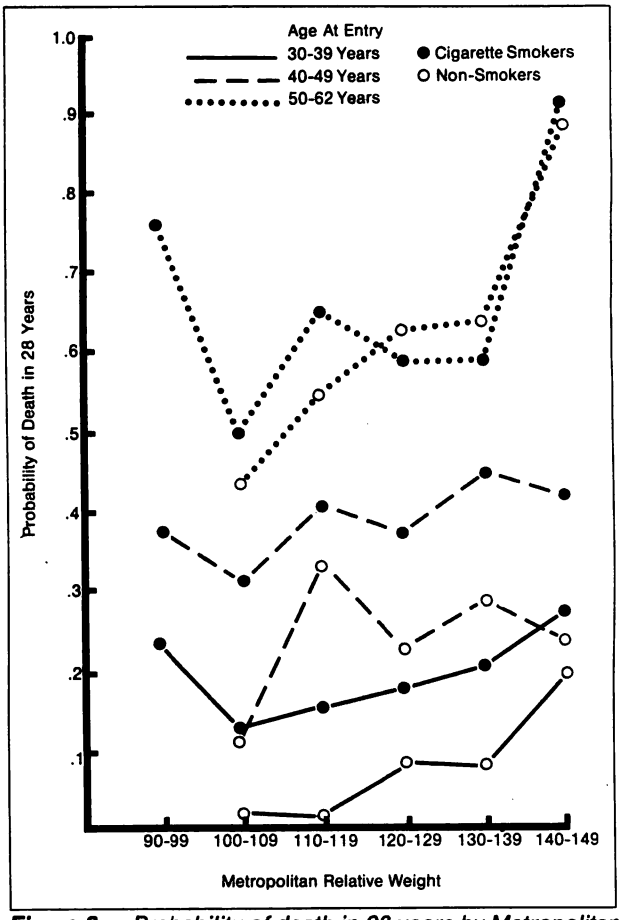

Figure 8. Probability of death in 28 years by Metropolitan relative weight in the general population and after removal of the cigarette-smoking men. The Framingham Heart Study.

Factors Unrelated to the Incidence of Coronary Heart Disease. Coffee, sleep, educational status, marital status, alcohol intake, percent greyness of hair, percent baldness, and socioeconomic status were not related to the incidence of coronary heart disease.

TABLE VI **Association Between Metropolitan Relative Weight (MRW) at Entry and Coronary Heart Disease Incidence by Length of Follow-Up in Framingham Men and Women**

	Multivariate Logistic Regression Coefficients for MRW			
Length of Follow-Up (years)	Men (n = 2,197)	Number of Events	Women (n = 2,714)	Number of Events
6	0.006	(114)	0.011	(56)
8	0.014*	(154)	0.008	(78)
14	0.012†	(314)	0.008*	(166)
20	0.012‡	(480)	0.007*	(301)
26	0.012‡	(636)	0.008†	(437)

NOTE: Regressions include adjustments for age, systolic blood pressure, serum cholesterol, cigarettes a day, glucose intolerance, and electrocardiographic left ventricular hypertrophy at examination 1. n = the number of individuals at risk. The number of events at different follow-up times are given in parentheses. * = $p < 0.05$; † = $p < 0.01$; ‡ = $p < 0.001$ (coefficient is significantly different from zero).

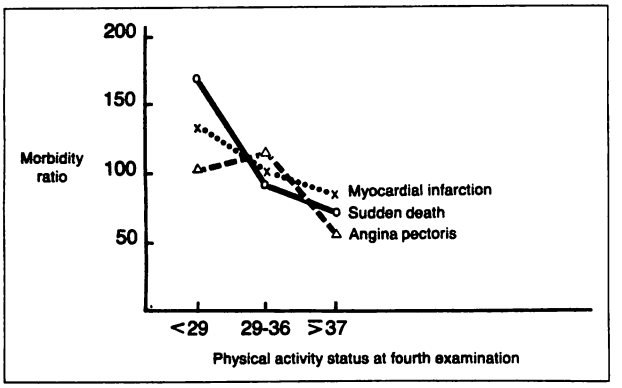

Figure 9. *Risk of developing coronary heart disease (10 years) according to physical activity index at fourth examination. Men aged 30 to 62 years at entry, Framingham Study.*

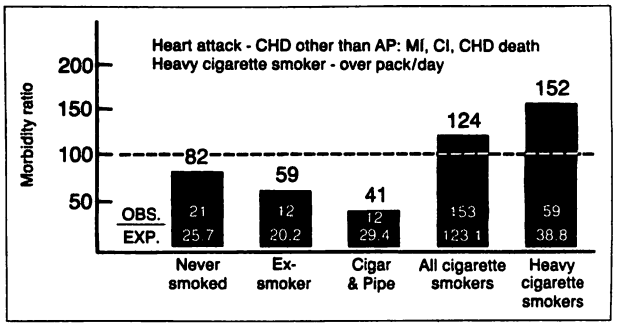

Figure 10. *Incidence of heart attacks in smokers. CHD = coronary heart disease; AP = angina pectoris; MI = myocardial infarction; CI = coronary insufficiency.*

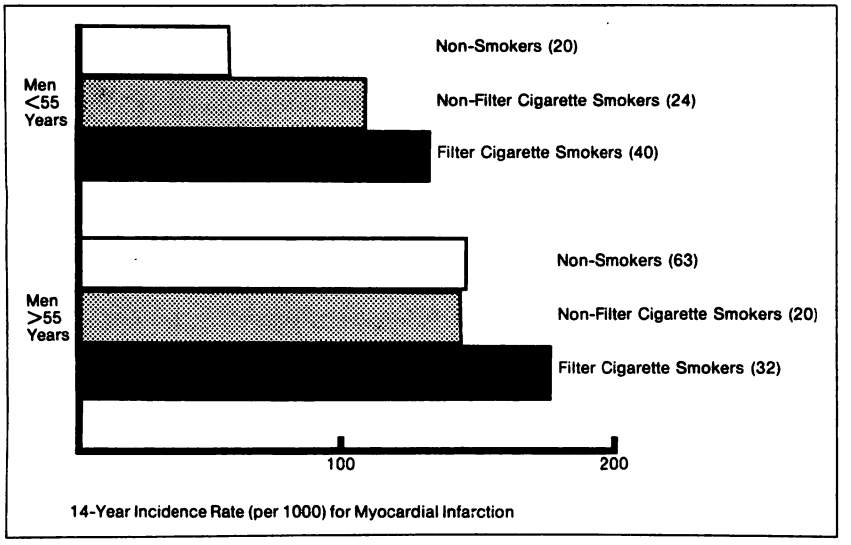

Figure 11. *Filter cigarettes and coronary heart disease, The Framingham Study. Rate per 1,000 for 14 years of observation following biennial examination 7 (1963–1964) for new myocardial infarction in men having no preexisting coronary heart disease at examination 7. The number of cases are given in parentheses for each group.*

Composite Score. **Figure 13** shows that putting several risk factors together compounds the risk. In the upper quintile of risk are found 80 percent of the strokes, 75 percent of the congestive heart failure, and roughly half the peripheral vascular and coronary heart disease.

COMMENTS

The preceding results indicate that there are a series of markers which, for the most part, will indicate to a physician the person in whom some form of cardiovascular disease is likely to develop in the future. Can reversal of any or all of these traits change the course of this disease?

With regard to lowering the cholesterol level we have both primary and secondary prevention trials in which either diet or drugs were used to accomplish this. Although many people say they are unimpressed by the results of such trials, in every single trial there was a decrease in the subsequent rates of coronary heart disease that was proportional to the decrease in total cholesterol; with as low as a 1 percent fall in cholesterol, there was a fall of 2 to 3 percent in the subsequent rates of coronary heart disease (**Table VII**).

These falls generally occurred within a five to seven year period. Although these changes are not all statistically significant the consistency of such a finding is impressive. What were the cholesterol levels in the treated group? In the first Oslo trial [9] treatment lowered the subjects' cholesterol level from 296 to 244 mg/dl; 244 is the average cholesterol level of a man in Framingham (and generally elsewhere) who gets a heart attack. Although such men did better, we remained unimpressed with the results of this trial.

Again, in most of the antihypertensive trials the

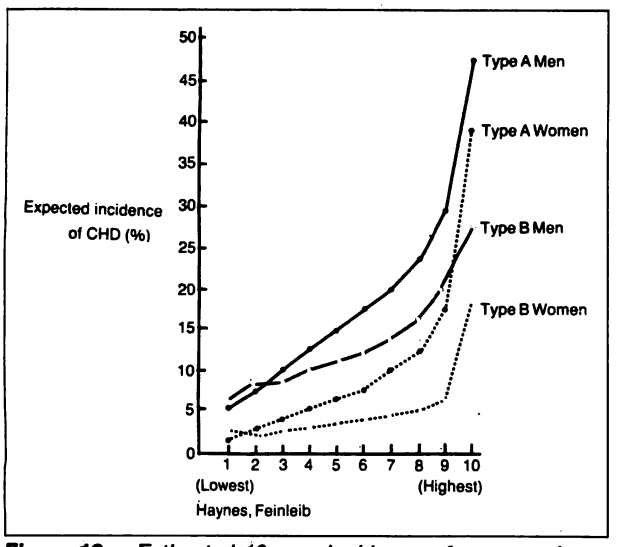

Figure 12. *Estimated 10-year incidence of coronary heart disease among Framingham type A and type B men and women, according to deciles of risk, based on the standard coronary risk factors.*

TABLE VII Percentage Fall in Coronary Heart Disease Rates in Various Cholesterol Lowering Trials

	Fall (Percent)
Diet	
Primary prevention	
N.Y. Anticoronary Club [10]	50
Helsinki Trial [11]	50
Leren (Oslo) [12]	44
Multiple Risk Factor Intervention Trial	7
Los Angeles Domiciliary (older men) [13]	25
Secondary prevention	
Leren (Oslo) [9]	35
Medical Research Council [14]	17
Drugs	
Newcastle Trial [15]	39
Scottish Society [16]	19
Coronary Drug Trial [17] (on nicotinic acid)	25
WHO [18]	20
Krasnow (United Airlines) [19]	65
Colestipol Trial [20]	60
Gemfibrozil [21]	73

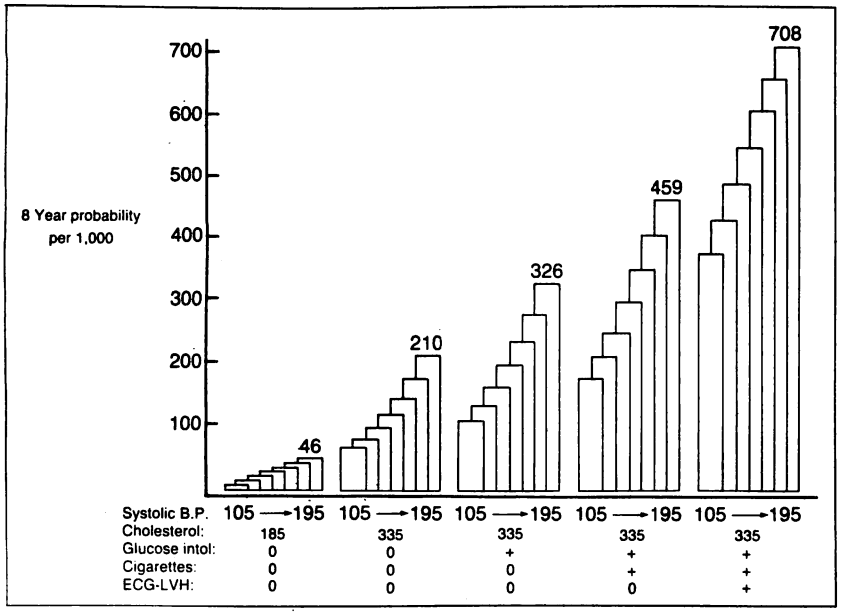

Figure 13. *Risk of cardiovascular disease according to systolic blood pressure at specified levels of other risk factors. Men aged 40 years; Framingham study, 18-year follow-up.*

treated group in the short term did have a significant decrease in the rate of stroke endpoints. The coronary heart disease endpoints fell but never reached statistically significant levels. The concern is what will happen to these people in the long term. Will some of the unfavorable changes in blood lipids seen with diuretic and beta-blocker therapy interfere with our management of the lipid abnormalities seen in many of these patients and diminish our ability to prevent their coronary attacks?

Coronary heart disease is a multifactorial disease but, of all the factors, the lipids are the most fundamental to the basic process. In Japan where blood pressure levels and smoking are very high, coronary disease was rare because their cholesterol levels were so low; apparently with a change in fat intake from 20 to 30 g 15 to 20 years ago to almost 60 g a day now in the metropolitan areas of Japan, coronary disease is on the rise.

Isolated management of one risk factor is poor medicine, and attention must be focused on all the major factors if the short- and long-term goals are to be kept firmly in mind, or if coronary heart disease is to be significantly reduced.

REFERENCES

1. Multiple Risk Factor Intervention Trial Research Group: Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. JAMA 1982; 248: 1465–1477.
2. Abell LL, Levy BB, Brodie BB, et al: A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J Biol Chem 1952; 195: 357.
3. Kessler G, Lederer H: Fluorometric measurements of triglycerides. In: Skeggs LT Jr., ed. Technicon Symposia Automation in Analytical Chemistry. New York: Medicad Incorporate, 1965; 341–344.
4. Burstein M, Samaille J: Sur un dosage rapide du cholesterol lie aux alpha et aux beta-lipoproteins du serum. Clin Chim Acta 1960; 5: 609.
5. Nelson N: A photometric adaptation of the Somogyi method for the determination of glucose. J Biol Chem 1944; 153: 375–380.
6. Gordan T, Kannel WB: Introduction and general background. In: Kannel WB, Jordan T, eds. The Framingham Study, section 1, U.S. Government Printing Office, Washington, 1968.
7. Walker SH, Duncan DB: Estimation of the probability of an event as a function of several independent variables. Biometrika 1967; 54: 167.
8. Snedecor GW, Cochran WG: Statistical methods. Ames IA, eds. Iowa State University Press, 1967.
9. Leren P: The Oslo diet-heart study—eleven year report. Circulation 1970; 42: 935–942.
10. Christakis G, Rinzler SH, Archer MS, et al: The anti-coronary club. A dietary approach to the prevention of coronary heart disease—a seven year report. Am J Pub Health 1966; 56: 299–314.
11. Miethinen M, Turpeinen O, Karvonen MJ, Elosus R, Paavilianen E: Effect of cholesterol lowering diet on mortality from coronary heart disease and other causes: a 12 year clinical trial in men and women. Lancet 1972; II: 835–838.
12. Hjermann I, Holme I, Byre KV, Leren P: Effect of diet and smoking on the incidence of coronary heart disease. Lancet 1981 II: 1303–1310.
13. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Toniyasu U: A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. Circulation 1969; 39,40 (suppl 2): 1–63.
14. Medical Research Council: Controlled trial of soya-bean oil in myocardial infarction. Report of a research committee to the British Medical Research Council. Lancet 1968; II: 693–699.
15. Physicians of the Newcastle-upon-Tyne Region: Trial of clofibrate in the treatment of ischaemic heart disease. Br Med J 1971; 4: 767–774.
16. Research Committee of the Scottish Society of Physicians: Ischaemic heart disease: a secondary prevention trial using clofibrate. Br Med J 1971; 4: 775–784.
17. Coronary Drug Project Research Group: Clofibrate and macin in coronary disease. JAMA 1975; 231: 360–381.
18. Committee of Principal Investigators: A cooperative trial in the prevention of ischaemic heart disease using clofibrate. Br Heart J 1978; 40: 1069–1118.
19. Krasno LR, Kidera GJ: Clofibrate in coronary heart disease. JAMA 1972; 219: 845–851.
20. Dorr AE, Gundersen K, Schneider JC Jr, Spencer TW, Martin WB: Colestipol hydrochloride in hypercholesterolemic patients effect on serum cholesterol and mortality. J Chron Dis 1978; 31: 5–14.
21. Mannimen M, Malkonen A, Eisalo J, et al: Gemfibrozil in the treatment of dyslipidemia. A five year follow-up study. Acta Med Scand 1982; 668 (suppl): 82–87.

Intervention for the Prevention and Control of Hypertension and Atherosclerotic Diseases: United States and International Experience

JEREMIAH STAMLER, M.D.
ROSE STAMLER, M.A.
Chicago, Illinois

Intervention to control hypertension and prevent coronary heart disease was initially undertaken in the United States in the late 1950s. It was conducted along three lines: randomized controlled trials, community demonstration projects, and broad public health and medical care efforts involving both the general population and its high-risk strata. This article reviews findings from the United States trials, particularly those on the primary prevention of coronary heart disease by unifactorial means (such as fat-modified diet, serum cholesterol-lowering drugs, antihypertensive drug treatment) and by multifactorial interventions. Results of unifactorial and multifactorial trials are discussed with reference to the prevention of high blood pressure. Studies in the United States are compared with research abroad, and current research needs are reviewed together with the implications for medical practice and public health. The United States population as a whole has a large high-risk segment. Since the late 1950s, significant population-wide changes have occurred in life-styles (diet, smoking, exercise habits), and this is especially true of the more educated. The proportion of persons with detected, treated, and controlled high blood pressure has risen markedly in all population strata. Consequently, a favorable shift has occurred in the population distribution of the major established risk factors: "rich" diet, hypercholesterolemia, high blood pressure, and cigarette smoking. It can be reasonably inferred that the steady and marked declines in death rates in the United States from coronary heart disease, stroke, all cardiovascular diseases, and all causes since 1968 are related to reductions in these risk factors.

Two aspects of the United States experience with respect to control of hypertension and prevention of atherosclerotic diseases (particularly epidemic coronary heart disease) are the clinical trials designed to assess efficacy of unifactorial and multifactorial intervention and the general experience in the population. This review focuses on primary prevention, that is, prevention of the first clinical manifestations of these diseases.

This article does not review coronary heart disease secondary prevention trials of platelet-influencing drugs, anticoagulants, beta blockers, antiarrhythmic agents, calcium channel blockers, coronary bypass graft surgery, ileal bypass to lower serum cholesterol, or exercise. No mention is made of trials of diet or drugs for coronary heart disease prevention in diabetic patients or the possible role in the control of high blood pressure of exercise or interventions to influence the central nervous system (for example, yoga, biofeedback, muscle relaxation, meditation).

From Northwestern University Medical School, Chicago, Illinois. Requests for reprints should be addressed to Dr. Jeremiah Stamler, Department of Community Health and Preventive Medicine, Northwestern University Medical School, Chicago, Illinois 60611.

Efforts to achieve control of hypertension and primary prevention of atherosclerotic diseases are based on ability to influence etiologic and pathogenetic mechanisms, and thereby affect the natural history of these diseases, in order to break links in the chains of causation. Rich diet, cigarette smoking, sedentary habit, and psychosocial stresses and tensions are examples of the modern "disturbances in human culture" [1] that lead to coronary heart disease. Rich diet is of central importance, since it leads to hypercholesterolemia or hyperbetalipoproteinemia and hypertension, two of the established major risk factors for atherosclerotic disease. Furthermore, rich diet promotes severe obesity and type II diabetes, which are risk factors for both hypertensive and atherosclerotic diseases. The role of these factors has been extensively reviewed [2–21].

Trials of preventive intervention against hypertension and atherosclerotic disease are not, and cannot be, decisive tests on disease causation [20]. Direct tests of causation would require intervention to test ability to produce disease. For hypertensive and atherosclerotic diseases, this would require randomized controlled trials starting in infancy, with large sample sizes and tight control for all possible etiologic factors, sizeable difference between experimental and control groups (in only one test factor preferably), and long trial duration (decades) for assessment of end-point outcome. These would be the requirements, for example, for estimating high versus low sodium intake as a cause of hypertension or high versus low cholesterol-saturated fat intake in the etiology of coronary heart disease and the other atherosclerotic diseases. Such experiments on etiology are not feasible and are not ethically defensible.

Hence, trials of interventions against hypertensive and atherosclerotic diseases are preventive, testing ability to delay disease progression and, if possible, to stop or reverse it. Although such research may contribute to understanding of disease etiology, it cannot be the critical, decisive test. Preventive intervention may be too little and too late, and there may be the following additional difficulties: (1) the intervention is often unifactorial, whereas the disease is almost certainly multifactorial in its causation; unifactorial intervention may be inadequate to affect outcome, even though the variable under influence is significantly related to the etiology of the disease; (2) unifactorial intervention is in many cases pharmacologic, with a long-term benefit to risk ratio that may or may not be favorable with regard to decisive end points of clinical disease (for example, coronary heart disease) and death, even though the drug has a powerful influence on an etiologically involved intermediate variable. The experience with clofibrate for the primary prevention of coronary heart disease is a case in point [22–24].

Although trials can only contribute partly to an understanding of disease etiology, they can be most valuable for elucidating benefit to risk ratio, especially for interventions that are potentially harmful, such as drug treatments. Such trials can go beyond the simple and dangerous assumption that because a factor is related to disease, its change in a favorable direction must be beneficial to overall health.

All these difficulties, plus related issues of sample size, power, and adherence, can readily lead to false negative results in preventive trials. Intervention study findings must be evaluated in the context of data from all the research disciplines, and thus they will at times contribute to the understanding of etiology, even though they fail by themselves to furnish critical and decisive data [21].

PART I. TRIALS ON UNIFACTORIAL INTERVENTION FOR PRIMARY PREVENTION OF CORONARY HEART DISEASE

Trials of Fat-Modified Diets for the Primary Prevention of Coronary Heart Disease. In the late 1950s, several investigative groups in the United States concluded that existing evidence warranted the design of controlled trials to assess whether change in diet, particularly lipid modification to lower serum cholesterol, is effective in the primary prevention of coronary heart disease [2,3,6,9,11–14].

Los Angeles Veterans Administration Domiciliary Facility Study. The Veterans Administration study in Los Angeles was a double-blind randomized controlled trial involving 846 residents of a domiciliary facility. Men averaged 65.5 years of age at entry, and the majority were free of signs of definite coronary heart disease [25]. Moderate serum cholesterol reduction was effected and sustained for the active intervention group by institutional feeding of a fat-modified diet, low in saturated fat and cholesterol and high in polyunsaturated fat and total fat. This study recorded significant reductions (31 percent) over 8.5 years in incidence of severe atherosclerotic events (coronary, cerebral, peripheral) **(Table I)** [25]. Efficacy was more marked for those less than the median age at entry and those with higher serum cholesterol levels. Differences in event rates were significant for those with and those without signs of preexisting atherosclerotic complications. Rate of fatal atherosclerotic events was also significantly lower (31 percent) in the group receiving the fat-modified diet (Table I) [25]. However, the mortality rate from all causes was not sizeably different for the two groups. Evidence was also obtained that rate of cholelithiasis was significantly higher with the high polyunsaturated fat diet than the control diet [26].

New York Anti-Coronary Club. The Anti-Coronary Club trial in New York City (1957–1972) involved 1,113

TABLE I **Incidence and Mortality from Atherosclerotic Events of Los Angeles Veterans Administration Domiciliary Facility Study***

Event	Number of Events: Fat-Modified Diet (n = 424)	Number of Events: Control Diet (n = 422)	Difference (Percent)
Incidence			
Major CHD event	54	71	−23.9
Cerebral infarction	13	22	−40.9
Ruptured aneurysm	2	5	−60.0
Amputation	5	5	0.0
All men with severe atherosclerotic events	66	96	−31.3†
Mortality			
Sudden CHD	18	27	−33.3
All CHD	41	50	−18.0
Cerebral infarction	3	9	−66.7
Ruptured aneurysm	2	5	−60.0
Amputation	0	3	
All men with fatal atherosclerotic events	48	70	−31.4†

CHD = coronary heart disease.
* Study was conducted over 8.5 years.
† $p < 0.05$.

men (aged 40 to 59 years at entry) of whom 75 percent were originally free of evidence of coronary heart disease [27–32]. Nutritional intervention involved both weight reduction and dietary fat modification, with use of a diet low in saturated fat and cholesterol and high in polyunsaturated fat (after initial weight reduction). For active participants of the 50 to 59 year age group at entry, favorable findings were reported with regard to atherosclerotic disease event rates, particularly for coronary heart disease. However, given the lack of randomly assigned controls, these results must be assessed as encouraging, not definitive.

Minnesota Mental Hospitals Trial. The Minnesota trial, initiated in the late 1960s in mental hospitals, has presented only an oral report of its findings. A significant favorable outcome was achieved with regard to the atherosclerotic disease end point for men younger than 40 years of age at entry fed a serum cholesterol-reducing diet, low in saturated fat and cholesterol and high in polyunsaturated fat, compared with randomly assigned control subjects eating a usual American diet [33]. However, negative results were reported for older men and women.

The first trials of the effects of a single dietary factor on heart disease, two of them with institutionalized populations and a third with free-living participants, were all on a small scale, with sample sizes no larger than 2 percent of the estimated requirements for a trial of this type with reasonable power to detect an intervention effect. All of them recorded positive results with regard to primary prevention of atherosclerotic disease end points, but the findings were not definitive and unequivocal. This outcome is understandable, given the marked inadequacy of sample size, as well as other design problems, such as lack of a randomly assigned control group in one trial, advanced age of participants in another, and, in all three, use of a fat-modified diet high in polyunsaturates.

The encouraging but nondefinitive results of these trials, together with the similar outcome of the "first generation" diet trial in Europe (Finnish Mental Hospital Study [34,35]) are consistent with the extensive findings of all other research methodologies on the primary and essential etiologic role of rich diet in producing epidemic premature coronary heart disease in the western industrialized countries. The experiences of these trials illustrate the complexities of this methodology. The overall findings provide evidence of the scientific basis for recommendations for improving American eating habits [2,3,6,7,9,11–14].

National Diet-Heart Study. Unlike the preceding diet trials, the National Diet-Heart Study was relatively short-term and did not attempt to assess effects of its fat-modified diets on atherosclerotic disease end points [36]. It was undertaken in the early 1960s to investigate the feasibility of large-scale unifactor trials on primary prevention of coronary heart disease by dietary fat modification [36]. The trial involved several thousand middle-aged men from the populations of five cities (Baltimore, Boston, Chicago, Minneapolis-St. Paul, and Oakland) and several hundred patients in a Minnesota mental hospital. The feasibility of a double-blind design both for research with institutionalized and noninstitutionalized populations was explored. Double-blind design was achieved for the latter by use of special food stores supplying coded fat-modified foods to the par-

ticipants, in accordance with their blinded random assignment to study groups.

The trial demonstrated that the American food industry could produce a wide range of fat-modified products (processed meats, baked goods, dairy products, visible fats, egg substitutes) sizeably reduced in cholesterol and saturated fat compared with their usual equivalents. In terms of appearance, texture, and taste, the modified products were indistinguishable from their usual counterparts and were broadly acceptable to the general population [36]. Many of these products were subsequently made available on the general market. The National Diet-Heart Study also showed that it was possible to achieve considerable reductions in mean serum cholesterol in free-living and institutionalized middle-aged American men [36].

The final report of the National Diet-Heart Study presented sample size estimates for a five-year two-group study ranging from 60,000 to 250,000 [36]. Large-scale unifactor diet-heart primary prevention trials could not readily be performed double-blind with free-living Americans, except at very great cost. Later experience in Minnesota also indicated that the task of accruing and maintaining an adequate sample of institutionalized persons was forbidding [33]. As was noted in the 1971 report of the National Heart and Lung Institute Task Force on Arteriosclerosis, there were major concerns about the resources of money and manpower needed [37].

There were also serious uncertainties about the basic scientific feasibility of the study design. In particular, how was it possible to keep the two groups comparable with regard to all aspects of life-style except diet? The active intervention group, especially, might change habits of cigarette smoking and physical activity, and seek care for high blood pressure, thereby confounding systematic unifactorial intervention and affecting the original objective of a single-factor diet-heart trial. This problem could be avoided by excluding men with other risk factors (hypertension, cigarette smoking, gross obesity, and sedentary life-style). However, this would leave a group of persons at relatively low risk, requiring such a large sample size as to preclude the possibility of recruiting the necessary number of men. A definitive unifactor diet-heart study was not proposed. Instead, the Task Force recommended and the National Heart and Lung Institute implemented a Multiple Risk Factor Intervention Trial.

These problems exist with regard to all unifactor trials of change in life-style for the prevention of coronary heart disease, whether the intervention is in diet, smoking cessation, exercise, or modification of type A behavior.

Single-factor life-style trials on the primary prevention of coronary heart disease, including a "definitive" diet-heart trial, are no longer feasible in the United States. In fact, no efforts of this kind are currently in progress nor are there plans to mount such trials. Short of direct evidence from definitive large-scale unifactor trials, the practice of clinical medicine and public health—concerned with the primary prevention of epidemic premature atherosclerotic disease—must proceed based on appraisal of extensive research evidence concerning life-styles and coronary heart disease. Nutritional patterns are crucial; therefore, improved eating habits are basic to the long-term endeavor to control the modern epidemics of hypertensive and atherosclerotic disease.

TRIALS OF ANTIHYPERCHOLESTEROLEMIC DRUGS FOR PRIMARY PREVENTION OF CORONARY HEART DISEASE

Cholestyramine and Colestipol. One randomized controlled multicenter trial on the bile acid sequestering resin colestipol [38] involved 2,278 hypercholesterolemic persons (1,094 men, 1,184 women) aged 18 years and older (mean ages of men, 50.5; of women, 57.0). Hypercholesterolemia was defined as a fasting serum cholesterol level 250 mg/dl or higher on at least two of three biweekly examinations during the six weeks before randomization. Of all participants, 69 percent of the men and 79 percent of the women were free of evidence of clinical coronary heart disease at baseline. Mean net reduction in serum cholesterol over the three years of the trial was 30 mg/dl (37 and 7 mg/dl for the colestipol and placebo groups, respectively), from a baseline average of about 314 mg/dl, that is, a decrease of about 10 percent. After 1,419 person-years of follow-up for men free of coronary heart disease at baseline, there were 10 and 11 deaths in the colestipol and placebo groups, respectively. Numbers of deaths were also few overall for the women, 20 and 21 from all causes, nine and 10 from coronary heart disease for the colestipol and placebo groups, respectively. Thus, this study of short duration, small sample size, and low power yielded no evidence of a primary preventive effect of colestipol in hypercholesterolemic persons free of clinical coronary heart disease at baseline. However, for men with a history of coronary heart disease at entry, with 618 patient-years of exposure, six and 17 deaths were recorded in the colestipol and placebo groups, respectively, respresenting rates of 18 and 58 per 1,000; the difference in rates was statistically significant ($p \leq 0.02$).

The National Heart, Lung and Blood Institute Type II Coronary Intervention Study also found evidence of benefit from serum cholesterol reduction with bile acid sequestrant resin for persons with hyperbetalipoproteinemia and a history of coronary heart disease [39]. The 143 participants were randomized to cholestyra-

mine or placebo, and serial coronary angiocardiograms were used to assess effect of serum cholesterol reduction on coronary atherosclerosis during five years of follow-up. Both groups were given nutritional advice to improve plasma lipid-lipoprotein patterns. Low-density lipoprotein cholesterol was 21 percent lower in the resin than in the placebo group. Progression of coronary atherosclerosis was less in the resin group [39A]. The greater the decreases in the low-density lipoprotein cholesterol and increases in high-density lipoprotein cholesterol, the less the progression of atherosclerosis [39B].

The multicentered Lipid Research Clinics Coronary Primary Prevention Trial in the United States and Canada published reports on its end-point findings in early 1984. This double-blind controlled trial involved 3,806 participants with hypercholesterolemia (hyperbetalipoproteinemia) randomized to cholestyramine or placebo. Both groups received advice concerning dietary fat modification to lower serum cholesterol [40]. Follow-up averaged 7.4 years. The cholestyramine group averaged considerably greater decreases in plasma total cholesterol and low-density lipoprotein cholesterol than the control subjects. Correspondingly, the cholestyramine group had a 19 percent lower rate of nonfatal myocardial infarction plus coronary death ($p < 0.05$), the trial primary end point. Incidence rates for new positive exercise tests, angina, and coronary bypass surgery were lower for the cholestyramine group by 25, 20, and 21 percent, respectively [40A]. Men with greater reductions in total cholesterol and low-density lipoprotein cholesterol in the cholestyramine group had much greater reductions in coronary incidence than men with lesser decreases [40B].

Other Recent Drug Studies. Recent studies, short-term and of small sample size, have shown that combinations of drugs are highly effective in markedly lowering and often normalizing severe hypercholesterolemia in persons with heterozygous familial hyperbetalipoproteinemia. This has been demonstrated with nicotinic acid and colestipol [41,42] and with the cholesterol synthesis blocker compactin plus resin [43]. No data are available on the long-term benefit to risk ratio of these drug combinations for such high-risk persons.

Careful dietary counselling is the safe treatment of choice for most persons with hyperlipidemia in the general population, since the primary cause of the hyperlipidemia is habitual ingestion of a diet excessive in cholesterol, saturated fat, and calories. Improved eating habits, along Mediterranean and Far Eastern lines (without high sodium content), can normalize all components of abnormal plasma lipid-lipoprotein pattern and contribute to control of high blood pressure as well.

TRIALS OF EXERCISE FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE

No unifactorial large-scale primary prevention trial of exercise intervention has been reported. The few studies conducted have been feasibility or pilot trials of small sample size [44–47]. One of the problems has been difficulty in maintaining active long-term participation by volunteers, especially in supervised exercise programs. Another problem is the difficulty of maintaining an exercise trial as a pure unifactorial study.

No large-scale trial on the role of exercise in the primary prevention of coronary heart disease can be anticipated. Medical care and public health must base their practice on best judgement of the available evidence from other sources. Epidemiologic, clinical, pathologic, and animal-experimental data suggest that in western industrialized countries, where there is a high prevalence of rich diet and cigarette smoking, sedentary life-style is yet another cultural disturbance resulting from 20th century socioeconomic developments. It is reasonable to encourage regular, frequent, moderate rhythmic (isotonic) exercise in leisure time as one component of better living habits for general health maintenance, health promotion, control of blood pressure, and coronary heart disease prevention.

EFFECTS OF SMOKING CESSATION ON INCIDENCE OF CORONARY HEART DISEASE

No unifactorial randomized controlled trials on prevention of coronary heart disease by cessation of smoking have been performed in the United States. However, extensive data are available from American population studies on the long-term prognosis of persons who stop smoking cigarettes, compared with those who never smoked and those who are current smokers [2,3,5,12,48–57]. Persons who stop while still in reasonably good health have a progressive reduction in risk of coronary heart disease and the other atherosclerotic and cardiovascular diseases, which approaches and eventually reaches levels of those who have never smoked. Data indicate that this is true for men and women of all ages. The fewer cigarettes formerly smoked per day and the earlier smoking was stopped, the more rapid the return to the risk level of a person who has never smoked. Benefit can be expected from stopping smoking, regardless of the number of years or how many cigarettes per day a person has smoked or the age of the person.

Cigarette smoking is one of the established major risk factors for coronary heart disease. Unequivocal proof has been provided for the important role of smoking in the etiology of premature severe atherosclerotic disease and its clinical sequelae, which are epidemic in the western industrialized countries.

cium) lowered blood pressure of normotensive young men and women by 6 and 9 percent, respectively [119].

Magnesium Supplementation Trial. Supplementation of the diet with magnesium has been reported to have an antihypertensive effect [120]. This trial involved 39 patients receiving long-term treatment with oral diuretics for high blood pressure or congestive heart failure or both. Twenty patients were randomly assigned to the treatment group and received 15 mmol per day (365 mg) of magnesium as aspartate hydrochloride. After six months, blood pressure had decreased to 140/85 mm Hg from 152/92 at baseline ($p < 0.001$); no blood pressure change was recorded for the control group. Plasma and urine electrolytes did not change significantly in the experimental group, nor did body weight.

Cessation of Heavy Drinking. There is one study on the effects on high blood pressure of cessation of heavy drinking [121]. Of a group of patients admitted to an alcoholic treatment facility, a high proportion were initially hypertensive. Blood pressure decreased to normal levels almost uniformly during the weeks immediately after the acute withdrawal phase. For those who abstained over the next 12 months, normotension continued, without need for drugs.

PART IV. TRIALS ON CONTROL OF HYPERTENSION BY MULTIFACTORIAL DIETARY MEANS

Weight Reduction and Decreased Sodium Intake. Weight reduction and decreased sodium intake have been investigated in consecutive order [98]. The data indicate an additive independent effect of the two interventions in obese persons with borderline high blood pressure.

Decreased Sodium and Increased Potassium Intake. A study involved two experiments, one with combined low sodium and high potassium intakes and the other designed to differentiate the effects of these two interventions [122]. The data indicate that persons with average baseline diastolic blood pressure of 90 to 110 mm Hg responded significantly to the combined regimen, and that the combination was more effective than low sodium alone. A supplement of 100 mmol of potassium enhanced the blood pressure-lowering effect of a sodium-reduced diet.

The combination of moderate restriction of sodium intake (down from 200 at baseline to 50 mmol per day) and high potassium intake (up from 80 at baseline to 200 mmol per day) lowered blood pressure of normotensive young adults and decreased pressor response with mental stress and with norepinephrine infusion [123,124].

Coronary Prevention Evaluation Program. The Chicago Coronary Prevention Evaluation Program included a subgroup of middle-aged men with high blood pressure. For these men with diastolic blood pressure of 90 mm Hg or higher at the end of a long control period, the multifactorial intervention program, already described, was associated with marked and significant reductions in systolic blood pressure and diastolic blood pressure, which were sustained for years [81]. Bivariate regression analysis showed a highly significant relationship between weight loss and blood pressure reduction, but there was no clear association between slowing of the pulse and blood pressure reduction.

Shift to Mediterranean-Type Diets. United States and Finnish studies have explored the effects on blood pressure in normotensive and/or hypertensive persons of dietary modification with use of a typical Mediterranean diet. The results have recently been summarized [125,126]. With a reduced total fat intake (to 23 percent of calories) saturated fat was considerably lowered, whereas polyunsaturated fat was maintained or increased to achieve a polyunsaturated to saturated ratio of 1.0 [113,125–127]. A significant decrease in blood pressure was reported for healthy middle-aged men and women. It was inferred that the effect was caused by dietary linoleic acid and was mediated through prostaglandins.

In two recent Finnish trials, the composition of the diet was explicitly modified to resemble the diet followed in Mediterranean countries [113,127]. The emphasis was not only on lower intake of fat-rich animal products (dairy foods and Finnish visible fats) and increased intake of products high in polyunsaturates, but also on greater consumption of vegetable products. Thus, several explanations are possible for the reported decrease in blood pressure: reduced dietary calories, total fat, saturated fat, and cholesterol; increased polyunsaturated fat, polyunsaturated to saturated ratio, vegetable products, and fiber. The findings of the National Diet-Heart Study discussed earlier are noteworthy. This trial achieved and sustained increases in polyunsaturated fat and polyunsaturated to saturated ratio in its experimental groups compared with controls. However, no intergroup differences in blood pressure were observed, that is, there was no evidence that high polyunsaturated fats and/or high polyunsaturated to saturated ratio lowered blood pressure in general population samples [36].

Shift to a Lacto-Ovo-Vegetarian Diet. A recent study reported that a lacto-ovo-vegetarian diet, of the type consumed by Seventh Day Adventists, lowered blood pressure of healthy normotensive volunteers by 5 to 6 mm Hg systolic and 2 to 3 mm Hg diastolic [128]. The effect was not thought to involve changes in dietary sodium or potassium; the key nutrients were regarded as unknown.

Hypertension Control Program. In the last few years,

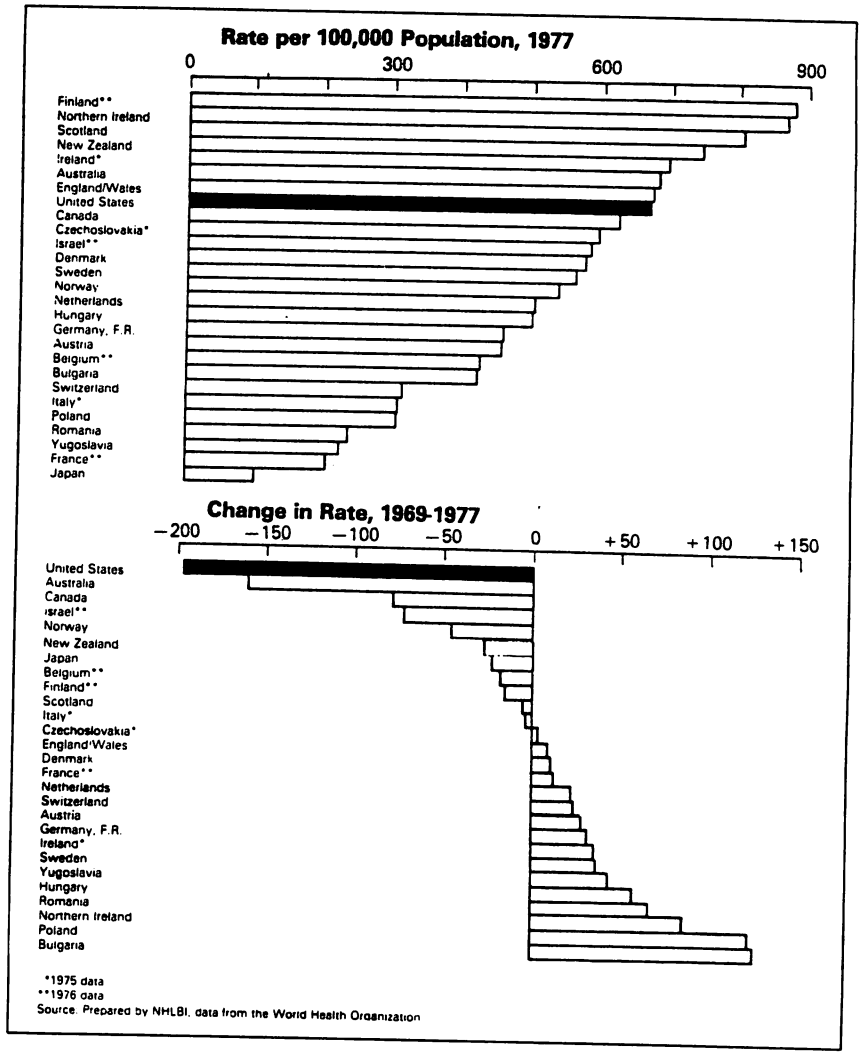

Figure 4. *Death rate for coronary heart disease by country, 1977 (**Top**), and change in death rate, 1969 to 1977 (**Bottom**), for men 35 to 74 years of age.*

causes have also been reduced. For coronary heart disease, this decline represents a reversal of rising rates that prevailed for decades for white and black men and for black women [12]. For stroke, the decline in the 1970s was a marked acceleration of a trend that began earlier. Over the decade 1969 to 1978, lives saved in the 35- to 74-year age group numbered more than 800,000, owing to the progressive decline in cardiovascular disease death rates. Evidence is mounting that declining death rates reflect decreases in severity of disease and in incidence of nonfatal and fatal events.

Supported by the findings from all the research methodologies, including randomized controlled trials, it is reasonable to infer that the changes in life-styles and risk factors, including those affecting high blood pressure and its control, have contributed significantly to the steady and marked decline in mortality rates from coronary heart disease, stroke, all cardiovascular diseases, and all causes in the United States since the late 1960s. It is reasonable to infer that the pace-setting efforts since the late 1950s that have encouraged better life-styles and control of high blood pressure are related to the fact that the declines in the United States in coronary heart disease mortality exceed those for any other country; many nations registered increases in rates over these years (Figures 4 and 5) [12,137]. This progress must be the foundation for next advances, as must be the fact that the United States incidence and death rates from the hypertensive and atherosclerotic diseases (especially coronary heart disease) are still high; the epidemic has not yet been halted, despite these declines. Present-day complexities and challenges (for example, optimal treatment for persons with high blood pressure, especially the millions with diastolic blood pressure of 90 to 104 mm Hg) must be viewed in context as consequences of great progress

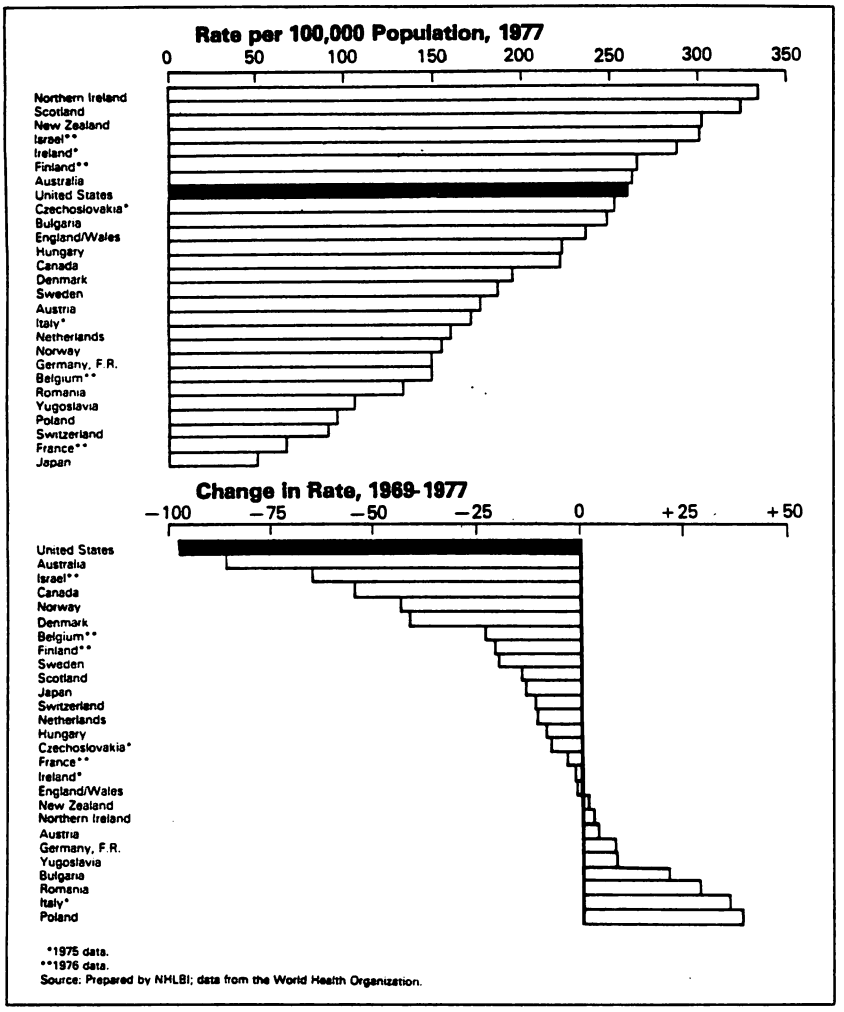

Figure 5. *Death rate for coronary heart disease by country, 1977 (**Top**), and change in death rate, 1969 to 1977 (**Bottom**), for women 35 to 74 years of age.*

in knowledge and its broad application, challenges on a new and unprecedently higher plane of endeavor against a mass disease problem. With this understanding as a foundation, continued progress in prevention and control will inevitably be registered, and with it major new gains in conquering the epidemic.

ACKNOWLEDGMENT

We are most grateful to the principal investigators of the following studies, and their publishers, for permission to reproduce data: Veterans Administration Cooperative Trial on Antihypertensive Agents, especially Edward Freis, M.D.; the United States Public Health Service Hospitals Cooperative Study, particularly W. MacFate Smith, M.D.; the Hypertension Detection and Follow-up Program; the Multiple Risk Factor Intervention Trial; the Coronary Prevention Evaluation Program, particularly David M. Berkson, M.D., Eduardo Farinaro, M.D., Yolanda Hall, M.S., and Dorothy Moss, M.S.; American Heart Association; Journal of the American Medical Association; and New England Journal of Medicine.

Our research has been supported by the American Heart Association; Amoco Foundation; Best Foods Research Center, A Division of CPC International, Inc.; Chicago Health Research Foundation; Chicago Heart Association; CIBA-GEIGY; Regional Medical Program of the Department of Health, Education, and Welfare; Marstellar (Flora Information Service); Nabisco Brands; and the National Heart, Lung, and Blood Institute.

Treatment Goals in Hypertension

ALBERTO ZANCHETTI, M.D.
Milan, Italy

Since the realization that hypertension was a risk factor for cardiovascular disease, methods of lowering elevated blood pressure have been developed. The main goal of antihypertensive treatment is to prevent or to arrest cardiovascular damage. Based on the successes and failures encountered for over 30 years or more of therapeutic experience in hypertension, several treatment goals have been established. Previously, it was claimed that the advantages of lowering blood pressure were not dependent on the antihypertensive drug used. Now, this is being questioned. For instance, fatigue is often observed in hypertensive patients treated with drugs that reduce cardiac output and limit peripheral blood flow. Is it therefore more rational to reduce blood pressure by returning increased vascular resistance to normal? Since antihypertensive therapy is life-long, we are becoming increasingly aware of the long-term effects (both beneficial and adverse) of antihypertensive drugs. The metabolic changes caused by current antihypertensive drugs are now being studied in detail. The potassium-depleting action of diuretics is well-known, and the significance of such an effect is being re-examined. The effects of various antihypertensive agents on serum lipids are relatively recent observations, the clinical importance of which is worthy of wider discussion and investigation. The abolition or reduction of all vascular complications of hypertension is the goal for which current antihypertensive treatment has most often failed. Whereas prevention of cerebrovascular accidents, renal failure, and heart failure has indeed been successfully achieved, coronary complications (the most frequent adjunct of hypertension) have been little influenced by antihypertensive therapy. Is this because coronary heart disease may be simply an associated disease, rather than a consequence of hypertension? Or is this because the beneficial action of the most widely used antihypertensive drugs on vascular disease is largely counteracted by unfavorable metabolic effects? These and similar questions have to be debated and resolved before we can define treatment goals more precisely and develop the most appropriate means to achieve them.

From the Center for Clinical Physiology and Hypertension, University of Milan, Ospedale Maggiore, Milan, Italy. Requests for reprints should be addressed to Professor Alberto Zanchetti, Centro di Fisiologia Clinica e Ipertensione, University of Milan, Ospedale Maggiore, Via F. Sforza 35, 20122 Milan, Italy.

In the last 30 years many advances have been made in the treatment of arterial hypertension. The development of the concept of high blood pressure being a quantitative derangement (that is, a risk factor for cardiovascular disease) rather than a disease itself has greatly encouraged these advances. This concept of hypertension as one risk factor is largely due to the imaginative work of George Pickering [1] and to some fundamental epidemiologic studies, such as the Fram-

ingham study [2] and the Metropolitan Life Insurance Company Data [3]. Once this concept was accepted, the obvious goal was the lowering of elevated blood pressure, on the expectation that, by whatever means blood pressure was lowered, this would help to prevent and arrest cardiovascular damage. The last 40 years have also seen an exceptional flourishing of pharmaceutical chemistry and chemotherapy, and as interest in lowering blood pressure has increased so has the pharmacologic means of controlling high blood pressure and treating arterial hypertension.

ANTIHYPERTENSIVE THERAPY—HEMODYNAMIC AND METABOLIC EFFECTS

For many years, the commonly accepted goal in the treatment of hypertension has been adequate lowering of blood pressure, and it has generally been assumed that the advantages achieved in lowering blood pressure did not depend on the characteristics of the antihypertensive drug used. All drugs appeared equally useful provided they were equally effective in lowering blood pressure. This approach has led to the numerous indisputable successes achieved by antihypertensive therapy in the last three decades. Nevertheless, the approach has also met with failures, and recognition of these failures may help to define more precise goals for antihypertensive therapy in the 1980s.

Available antihypertensive drugs differ greatly in mechanism of pharmacologic action and hemodynamic effects. Although the hemodynamic pattern of hypertension is characterized by a normal cardiac output and augmented peripheral vascular resistance, not all antihypertensive drugs act to reverse the pattern of circulatory dysregulation by returning peripheral resistance to normal. Compounds such as the beta blockers lower blood pressure by reducing cardiac output rather than vascular resistance [4]; although they are undoubtedly effective antihypertensive agents, it is possible that the unexpectedly high drop-out rate and the high incidence of complaints of fatigue in the propranolol-treated patients of the Medical Research Council trial [5] were caused by the reduction in cardiac output and peripheral blood flow. Thus the goal of lowering blood pressure by reducing peripheral vascular resistance without affecting cardiac output seems to be rational and should be tested.

Antihypertensive treatment is life-long. Until now, attention has been focused mostly on adverse effects that appear during relatively short-term therapy. This attention is by no means misplaced, as short-term adverse effects heavily influence patient compliance and obviously limit the longevity of successful antihypertensive therapy. However, only recently was the importance of the long-term effects (both beneficial and adverse) of antihypertensive drugs realized. The potassium-depleting action of diuretics is well known, and the significance of such an effect is presently under reexamination. Even relatively small decreases in serum potassium, long thought unimportant, have now been shown to facilitate life-threatening arrhythmias [6] and to be partly responsible for the reduced glucose tolerance often caused by diuretics. The effects of diuretics and beta blockers on serum lipids are recent observations; their clinical importance is worthy of wider discussion and investigation because some of the lipid changes observed are considered independent risks for the development of vascular disease.

PREVENTION OF CARDIOVASCULAR DISEASE BY ANTIHYPERTENSIVE THERAPY

Current antihypertensive treatment has often failed in its goal of preventing, arresting, or reversing *all* vascular complications of hypertension. Its success has been conspicuous but far from general. Cerebrovascular disease is the complication of hypertension most likely to benefit from antihypertensive therapy. Its successful prevention has been shown in the subjects with uncomplicated mild hypertension in the Australian study [7] and of the Hypertension Detection and Follow-Up Program [8]. Furthermore, the development of cardiovascular disease can be arrested; this was first suggested by the Veterans Administration Cooperative Study [9] on the basis of an almost complete disappearance of strokes in treated patients who had already experienced some vascular damage at entry into the trial. Arrest of the course of advanced cerebrovascular disease has been documented more crucially by showing that in treated hypertensive patients with transient ischemic attacks progression to completed strokes is less likely than in untreated hypertensive patients [10].

Prevention and arrest of renal damage has been observed repeatedly [9]. The effect on cardiac hypertrophy is a more complicated issue. There is evidence that it can be reversed, but not all antihypertensive drugs appear to be equally effective [11]. Obviously, more information is necessary on this important aspect of the treatment of hypertension.

ANTIHYPERTENSIVE TREATMENT AND THE INCIDENCE OF CORONARY HEART DISEASE

Coronary heart disease is considered the most frequent complication of hypertension [2], but prevention of coronary heart disease by antihypertensive therapy has continued to elude us. Indeed, the incidence of coronary heart disease was not reduced in the treated patients in the Veterans Administration Study [9]; in the Australian trial on mild hypertension [7], a lower incidence of deaths due to myocardial infarction was observed;

however, there was no difference in the incidence of nonfatal myocardial infarction and of other ischemic events. Suffice to say, the evidence concerning prevention of coronary disease is somewhat equivocal spanning from some favorable indications from the Hypertension Detection and Follow-Up Program [8] to no benefit or even unfavorable results in the Multiple Risk Factor Intervention Trial [12].

An understanding of why antihypertensive treatment has not significantly reduced the incidence of coronary heart disease to date is of utmost importance. All reasonable hypotheses should be explored. An iconoclastic explanation for this failure states that coronary disease might not be a consequence of hypertension but simply an associated disease. In principle, verification that cerebrovascular disease or coronary heart disease is a consequence of hypertension requires two sets of proof: (1) the incidence of damage in the two vascular areas increases with increasing blood pressure, and (2) the incidence of these conditions decreases when blood pressure is reduced. Statements (1) and (2) are proved to support cerebrovascular disease as a consequence of complication of hypertension. However, only statement (1) is proved in the relation of coronary disease to hypertension, and the hypothesis that the two may simply be frequently associated diseases cannot entirely be dismissed. For example, vascular disease, when not limited to coronary arteries, can cause the aorta and large vessels to stiffen and thus frequently elevate blood pressure.

An alternative hypothesis has been given increased attention recently. This hypothesis suggests that the prevention of coronary heart disease through therapy has failed because the antihypertensive drugs most widely used to date are efficacious in lowering blood pressure but have concomitant unfavorable metabolic effects. These and similar problems must be debated and resolved before we can define treatment goals more precisely and develop the most appropriate means to achieve them.

REFERENCES

1. Pickering GW: The nature of essential hypertension. London: J & A Churchill, 1961.
2. Kannel WB: On the cardiovascular hazards of hypertension. In: Onesti G, Klimt CR, eds. Hypertension: determinants, complications and intervention. New York: Grune & Stratton, 1979; 143–149.
3. Metropolitan Life Insurance Company: Blood pressure, insurance experience and its implications. New York: Metropolitan Life Insurance Company, 1961.
4. Lund-Johansen P: Haemodynamic consequences of long-term beta-blocker therapy: a 5-year follow-up study of atenolol. J Cardiovasc Pharmacol 1979; 1: 487–495.
5. Medical Research Council Working Party on Mild to Moderate Hypertension: Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Lancet 1981; II: 539–543.
6. Magnani B, Hansson L, Poole-Wilson PA, eds: Potassium, the heart and hypertension. New York: Transmedica, 1982.
7. Report by the Management Committee: The Australian therapeutic trial in mild hypertension. Lancet 1980; 1: 1261–1267.
8. Hypertension Detection and Follow-Up Program Cooperative Group: Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure including mild hypertension. JAMA 1979; 242: 2562–2571.
9. Veterans Administration Cooperative Study Group on Hypertension: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 1970; 213: 1143–1152.
10. Whisnant JP, Cartlidge NEF, Elveback LT: Carotid and vertebral-basilar transient ischaemic attacks: effect of anticoagulants, hypertension, and cardiac disorders on survival and stroke occurrence—a population study. Ann Neurol 1978; 3: 107–115.
11. Messerli FH, Schlant RC, eds: Left ventricular hypertrophy in essential hypertension. Mechanisms and therapy. Am J Med 1983; 75 (Suppl 3A): 1–116.
12. Multiple Risk Factor Intervention Trial Research Group: Multiple Risk Factor Intervention Trial. JAMA 1982; 248: 1465–1477.