THE RISKS FOR PREMATURE CARDIOVASCULAR DISEASE

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INTRODUCTION

"According to the Great Equation, Medical Care equals Health. But the Great Equation is wrong. More available medical care does not equal better health. The best estimates are that the medical system (doctors, drugs, hospitals) affects about 10 per cent of the usual indexes for measuring health: whether you live at all (infant mortality), how well you live (days lost due to sickness), how long you live (adult mortality). The remaining 90 per cent are determined by factors over which doctors have little or no control, from individual lifestyle (smoking, exercise, worry), to social conditions (income, eating habits, physiological inheritance), to the physical environment (air and water quality). Most of the bad things that happen to people are at present beyond the reach of medicine" (Wildavsky, 1977).

Wildavsky's statement is an oversimplification and overlooks the considerable successes that physicians and the medical care system have had in relieving suffering and pain, in preventing disability and in postponing death. The problem largely arises from the lack of suitable indices to measure the relief of suffering and the prevention of disability. The postponement of death is especially easy to miss. Since mortality figures are so available and so much more accurate than most other health statistics, they have been used (as does Wildavsky) as the primary indicators of medical success or failure. But a major success of modern medicine is the postponement of death from eventually fatal disease. Such postponement hardly shows up in the statistics. As Walsh McDermott has stated, "Death from serious heart disease cannot be indefinitely prevented. But with good physician care involving much science-based physiologic management, useful life, including full employability, may be extended for two or three or more years. With hundreds of thousands of deaths from heart disease each year in the U.S., however, deaths postponed from one period to another (say 1971 to 1974) cannot be distinguished from those occurring in the first year of the diagnosis. This great achievement of today's personal-encounter physician--the ability to modulate the deranged physiology of ultimately fatal chronic disease--is something for which we lack measures. Thus, there is no way such physician 'successes' can be detected in the box score of the public good. Today's oft repeated statement that what the physician does has relatively little influence on health is more correctly stated that what the physician does has relatively little influence on those indicators of health that are largely irrelevant to what he does" (McDermott, 1978)

Nonetheless, there is considerable truth to our relative ineffectiveness in controlling many societal and individual factors which determine health. We must be aware of what they are and should try to rid the bad things from society at large and diminish their impact upon individual patients. For good reason, there is increasing concern about the economic waste and limited effectiveness of "crisis" medicine which mainly deals with sick people near the end of their lives. The nature of the problem is seen in Figure 1: between 1940 and 1975, the

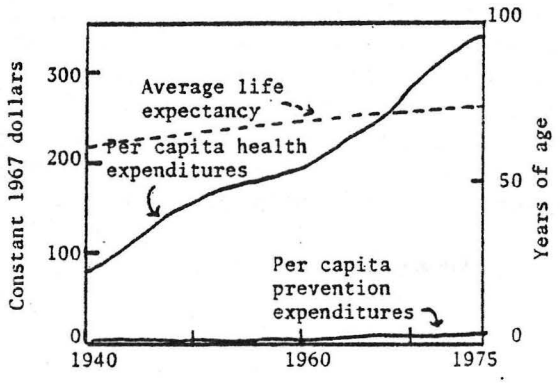


Figure 1

average life span increased 15% while per capita expenditures for disease care increased 314% in constant 1967 dollars (Gori and Richter, 1978). It has become obvious that much of the costs of disease care are the consequences of reckless personal and social habits such as smoking, improper diet, excessive drinking, drug abuse, lack of exercise, unsafe driving and working conditions and environmental pollution. With the recognition of the importance of these factors comes the recognition that preventive measures must be introduced to diminish their impact.

But as of now, little is being done. Note the virtually non-existent per capita expenditure for prevention of disease in Figure 1 and how little the curve has risen since 1940. Preventive medicine is little taught or practiced, particularly in a setting such as ours. Working in the Parkland outpatient clinic to identify and manage early hypertension cannot come close to the intellectual and emotional excitement of the coronary care unit. At Southwestern, 25 years ago, a significant part of the second year curriculum was given to a course entitled Preventive Medicine and Public Health. The course dealt largely with infectious diseases but it also covered the physical environment, social conditions and individual lifestyles--those factors which Wildavsky says determine 90% of health. Recalling the course, much seemed extraneous to what we needed to know. Spending half a day at the Dallas sewage disposal plant was largely a waste of time. But a good deal, in retrospect, was pertinent: discussions of the hazards of environmental pollutants, attempts to relate the conditions of west Dallas to the medical problems seen among Parkland's indigent patients, presentations on the importance of case-finding and eradication of venereal diseases.

For many years, no such course has been provided and preventive medicine has largely given way to molecular genetics and immunology. The Pediatricians still discuss immunization and OB-GYN emphasizes the need for improved prenatal care to prevent pregnancy-induced hypertension and other causes of fetal morbidity. But little more on preventive medicine can be found in the curriculum.

Part of the disaffection with Preventive Medicine arose when the earlier successes with communicable diseases failed to apply so simply to the cardiovascular and other diseases of a chronic nature which increasingly are responsible for death and disability. Two fundamental differences explain the failures: first, the infectious disease model is clean and straightforward, the cardiovascular disease model is confusing and ambiguous. In the words of Dr. Seldin, "One can identify the pneumococcus as a cause for pneumonia and eradicate it and the causal nexus is closed. Causal necessity has been at once identified, asserted, and the cause has been eliminated, resulting in the cure characteristic of a high technology" (Seldin, 1977). However, chronic cardiovascular diseases rarely fit this simple model. Multiple factors are likely responsible. Those involved are difficult to eradicate, requiring life-long personal intervention rather than short-term, external action. And this leads to the second difference: whereas pneumonia is sudden in onset and its cure takes only days, coronary artery disease takes decades to develop and may never recede. The distance in time and space between the interventions and outcome is the basic problem. As stated by L.W. Green, "For *society*, the distance in time is measured in discount rates, the inflationary value of future benefits relative to current costs, and the more 'urgent' medical needs of today...relative to the less urgent, less certain future benefits to be appreciated from preventive measures. For *individuals*, especially children and youth, this calculus of measuring the future benefits of today's sacrifice or investment in prevention is even more

difficult. For the young, the distance is greater, the benefits less certain, the imagination less experienced, the competing opportunities of the present more compelling, and the burden of the present investments in prevention seemingly more costly relative to the limited resources available to children and youth" (Green, 1978).

J.A. Muir Gray puts the problem in a different perspective: "I suggest that the main reason why people choose to act in a way that puts them at risk is because their concept of the future is different from that of those who give them advice. We ask people to desist from behavior which is immediately rewarding, offering as an alternative a reduction in the probability that they will become unwell in the future, the future being a decade or more from the point at which the decision must be made. People in (the lower) social classes, those most at risk, live and have been brought up in a culture in which time finishes next Friday. Job and house can be lost at the end of next week and savings can be spent in the first week or two or unemployment" (Gray, 1977).

Despite these inherent problems, a great deal of attention has been given during the past few years to a major aspect of preventive medicine--the recognition and management of risk factors for premature cardiovascular disease. This Grand Rounds will attempt to provide an up-to-date review of this area.

REFERENCES: *Introduction*

Gori GB, Richter BJ. Macroeconomics of disease prevention in the United States. Science 1978; 200:1126.

Green LW. The oversimplification of policy in prevention. AJPH 1978; 68:953.

McDermott W. Health impact of the physician. Am J Med 1978; 65:570.

Muri Gray JA. The failure of preventive medicine. Lancet 1977; 2:1339.

Seldin DW. Medicine within the vision of man. Presented at the University of Texas Southwestern Medical School, Sept. 30, 1977.

Wildavsky A. Doing better and feeling worse: the political pathology of health policy. Daedalus 1977; 106:105-123.

THE OVERALL STATUS OF RISK FACTORS

Humans have a maximum life span potential of about 95 years (Cutler, 1979). The likelihood that an individual will reach this age may be partly predetermined by heredity, at least among the children of people who live to be 90 or more (Abbott *et al*, 1978). On the other hand, in other studies, the hereditability of survival is nearly zero (Phillippe, 1978) with the conclusion that familial similarities in longevity largely arise from shared environments.

Life expectancy in 1979 is considerably below the presumed maximal potential and we in the U.S. are below most industrialized countries (Table 1). Most premature deaths are caused by cardiovascular (C-V) diseases which are responsible for more than half of all deaths (Figures 2, 3). Though more prevalent in those over 65, they are the single most common cause of death for those below 65 as well. Almost two-thirds of these are coronary events with stroke, congestive failure and renal insufficiency comprising the rest (Figure 4). As to overall morbidity, hypertension is most prevalent (Figure 5) and, as we shall see, is the major factor responsible for cardiovascular disease mortality.

TABLE 1

Trend in the Death Rate for Coronary Heart Disease; Selected Countries; Males Age 45-54 1970-1975

Country	Life Expectancy Male (1972-1974)	Life Expectancy Female (1972-1974)	Death Rate for Coronary Heart Disease; Males Age 45-54, 1975 (Per 100,000)	Percent Change Since 1970
Sweden	71.9	77.4	156.7	+14.8
Netherlands	71.2	76.9	194.8	- 3.3
Canada	69.8	76.6	245.5	- 9.1
England/Wales	69.3	75.3	290.9	+12.3
West Germany	68.2	74.3	158.7	+ 7.4
Australia	68.1	74.4	284.5	- 4.3
U.S.A. (white)	67.8	75.3	287.8	-13.4
Scotland	67.8	74.1	347.2	+ 1.2
Finland	65.9	74.0	420.5 (1974)	+ 4.4

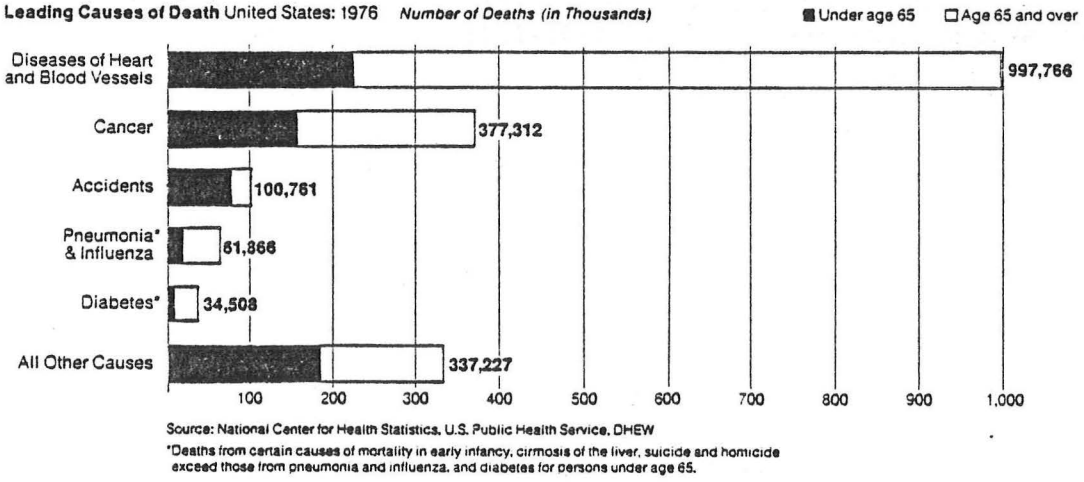


Figure 2

FIVE LEADING CAUSES OF DEATH IN THE U.S., 1900-1976

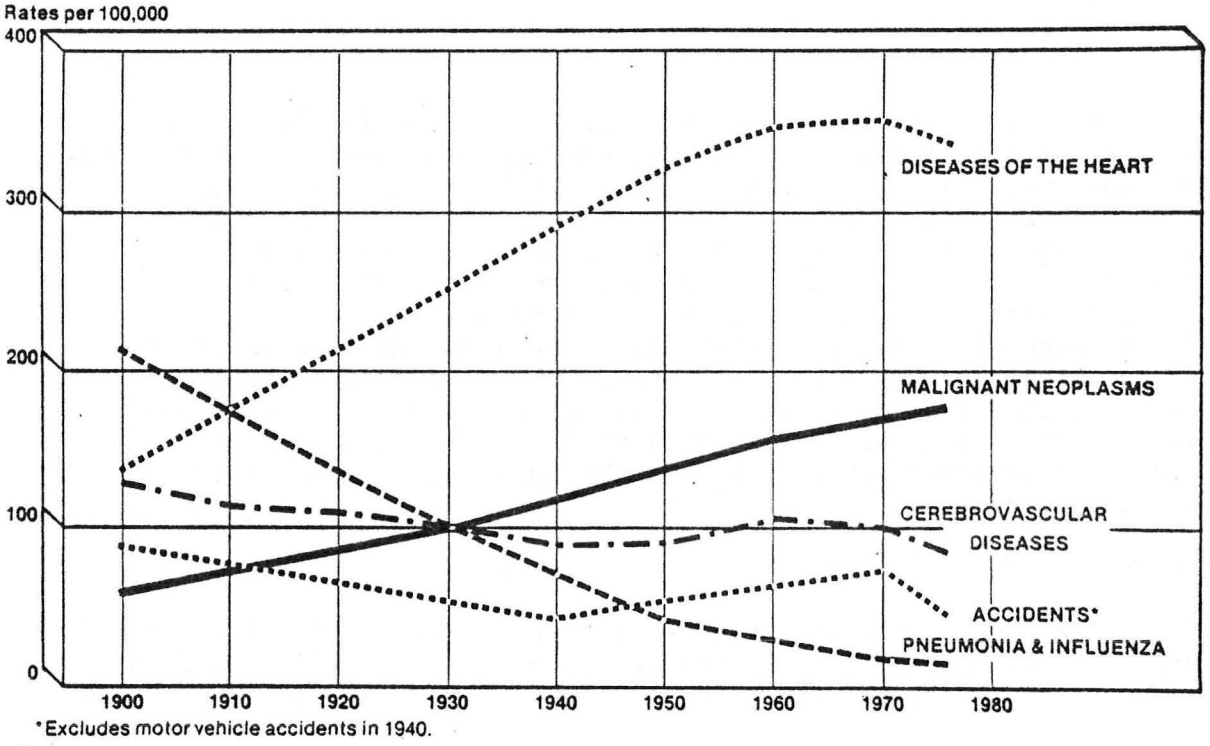
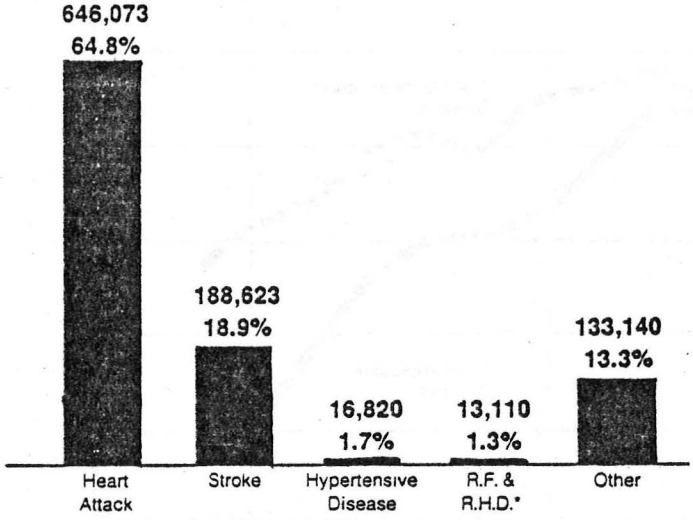


Figure 3

Deaths Due to Cardiovascular Diseases by Major Type of Disorder United States: 1976



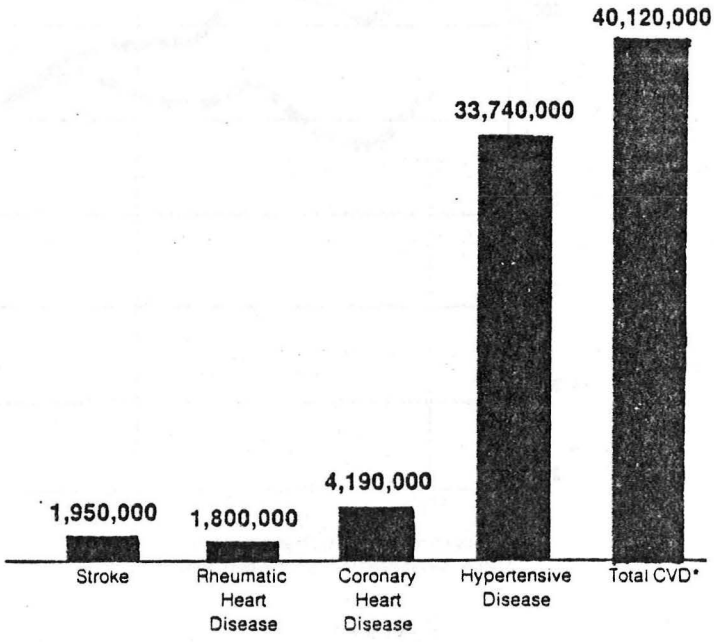
*Rheumatic Fever and Rheumatic Heart Disease

Source: National Center for Health Statistics, USPHS, DHEW

Figure 4

Estimated Prevalence of the Major Cardiovascular Diseases United States: 1976

*The sum of the individual estimates exceeds 40,120,000 since many persons have more than one cardiovascular disorder.



Source: American Heart Association

Figure 5

Since C-V diseases are the major cause of premature death, attempts have been made to determine the factors responsible for their development.

Epidemiological Studies

At least 5 large scale studies have been done over the past 30 years to examine the associations between various identifiable features and the risks for premature C-V disease (Pooling Project, 1978). All clearly define 3 factors to be primarily related: hypertension, hypercholesterolemia and smoking. Since the data from one of these, the Framingham Study, are representative of the rest and since these data have been most completely analyzed and widely disseminated, they will be considered in most detail.

First, each of these major risk factors will be examined as to its prevalence, mechanisms of inducing C-V disease and management. Second, other factors which may also be involved including glucose intolerance, obesity, sedentary activity and stress will be discussed. Third, the interactions of the three will be demonstrated. And lastly, an overall plan for future action will be presented.

The Good News Before the Bad

Since 1968, the mortality from C-V diseases, both heart attacks and strokes, has been falling both in the U.S. (Cooper *et al*, 1978) and, to a lesser degree, in Great Britain (Florey *et al*) (Figure 6). The improvement

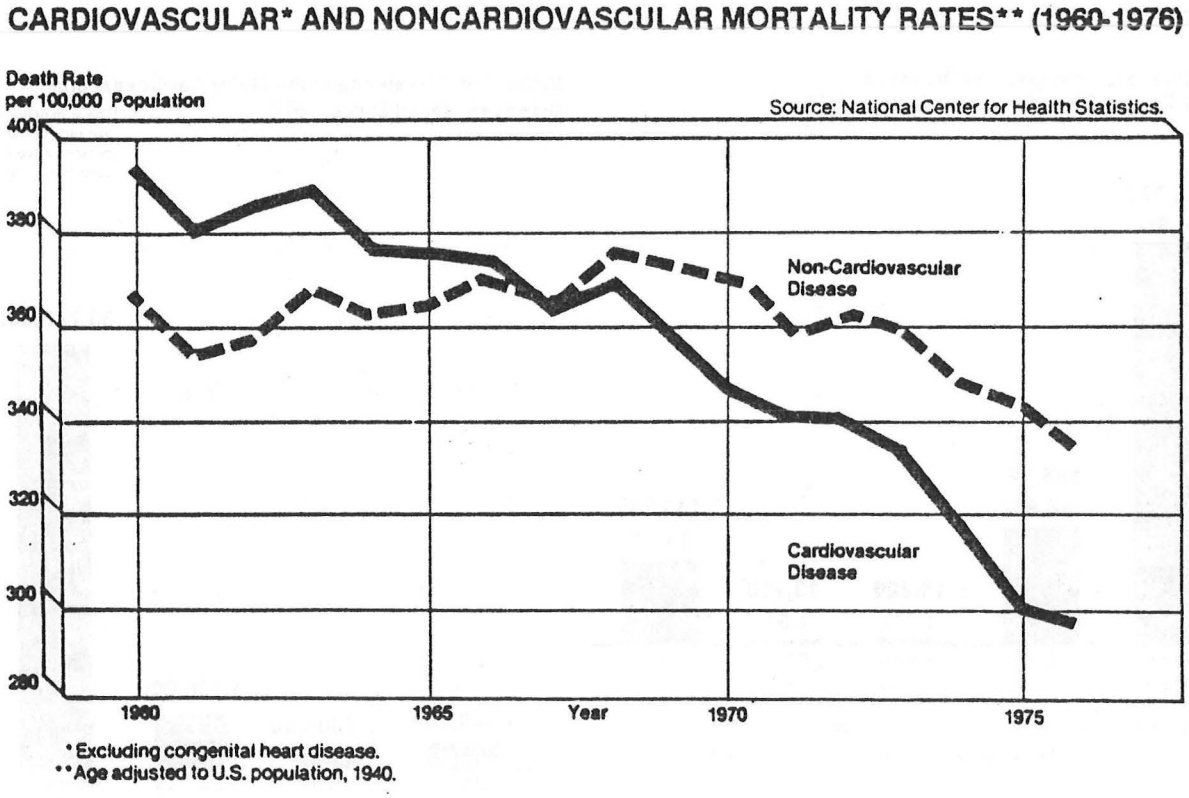


Figure 6

is particularly striking in blacks (ie. non-whites) (Table 2) and has also been found among Mexican-Americans in San Antonio (Stern and Gaskill, 1978). As a result, for the first time since such data have been accurately collected, life expectancy for the *adult* population has significantly increased (Figure 7, Table 3). Table 3 shows the data for white American males from 1900 to 1974. We still have a long way to go to reach 95 but the extra 3 or 4 years should be appreciated by all.

TABLE 2

Mortality rates, percent changes in mortality rates, and lives saved in 1975, by cause, age-sex-race, persons age 35–74, United States, 1968 to 1975

Cause of death	White male		White female		Nonwhite male		Nonwhite female	
	1968	1975	1968	1975	1968	1975	1968	1975
	Age-adjusted death rates per 100,000							
Coronary heart disease	883.4	719.2	349.2	266.7	974.2	689.7	651.5	424.0
Cerebrovascular diseases	157.0	117.8	112.8	83.7	372.1	233.7	334.3	190.1
All cardiovascular diseases	1,165.5	948.7	533.2	409.1	1,613.6	1,107.7	1,177.2	743.1
All causes	2,138.2	1,849.1	1,081.6	919.2	3,245.6	2,483.1	2,122.9	1,487.2
	Percent change in age-adjusted death rates, 1968–1975							
Coronary heart disease	−18.6		−23.6		−29.2		−34.9	
Cerebrovascular diseases	−25.0		−25.8		−37.2		−43.1	
All cardiovascular diseases	−18.6		−23.3		−31.4		−36.9	
All causes	−13.5		−15.0		−23.5		−29.9	
	Lives saved in 1975, attributable to fall in mortality rates, 1968 to 1975							
Coronary heart disease	45,000		25,000		8,000		8,000	
Cerebrovascular diseases	10,000		9,000		5,000		5,000	
All cardiovascular diseases	59,000		38,000		15,000		15,000	
All causes	80,000		51,000		23,000		23,000	

LIFE EXPECTANCY AT BIRTH BY BIRTH YEAR, 1960-1976

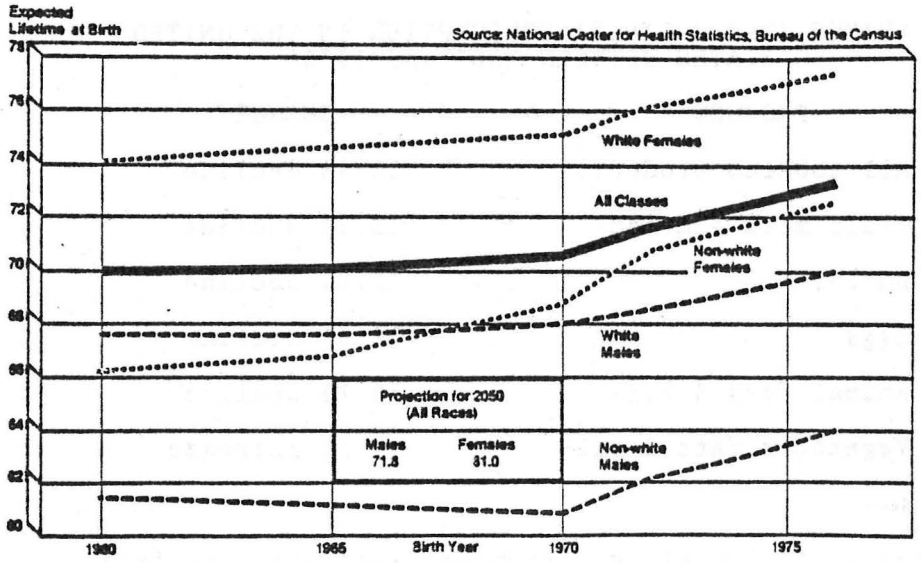


Figure 7

TABLE 3

Life Expectancy of White American Males by Age & Year

	YEAR			
	1900	1940	1970	1974
Birth	52.8	65.4	67.7	68.9
20	47.9	50.1	50.1	53.3
30	39.6	40.9	40.9	44.1
40	31.2	31.7	31.7	34.9
50	23.1	23.2	23.2	26.0
60	15.9	15.9	15.9	18.3

Data from Monthly Vital Statistics Report 24:No. 11, 1976
National Center for Health Statistics

Provisional statistics for 1978 show a slight *increase* in overall deaths (1,924,000 vs 1,898,000 in 1977) and in cardiovascular deaths (959,280 in 1978 vs 952,970 in 1977) though the number of deaths from stroke and hypertension continued to decline (National Center for Health Statistics, Vital Statistics Report, March 15, 1979).

Why this improvement? A number of changes in lifestyles and medical care are likely involved (Table 4). Based upon the recent changes in risk factor status for white American men, Stamler estimates the contributions to be roughly 50% by the decrease in cigarette smoking, 25% by the reduction in serum cholesterol and 25% by the better control of hypertension (Table 5) (Stamler 1979).

TABLE 4

CHANGE IN PER CAPITA CONSUMPTION IN THE UNITED STATES BETWEEN 1963 and 1975*

PRODUCT	CHANGE
All tobacco products	22.4% decline
Fluid milk & cream	19.2% decline
Butter	31.9% decline
Eggs	12.6% decline
Animal fats & oils	56.7% decline
Vegetable fats & oils	44.1% increase

*Figures for calculating percentage were obtained from U.S. Department of Agriculture.

Table 5

Contribution of Change in Individual Major Risk Factors to Expected Decrease in CHD for Middle-Aged White American Men, Based on Reported Recent Changes in Population Risk Factor Status

Variable	1950s to Mid-1970s	Change in CHD Mortality Accounted for by Decrease in Risk Factor
Serum Cholesterol- $\bar{X}$ -- mg/dl	235 → 220	28 %
Diastolic Pressure - $\bar{X}$ -- mm Hg	86.0 → 84.3	24%
Cigarette Smoking	55% → 40%	48%

Mortality from stroke has fallen most dramatically (Soltero *et al*). Beyond the uncertainty as to what's responsible for the decrease in *deaths* due to heart attack and stroke, another critical question remains unanswered: is the frequency of C-V *morbidity* also diminishing? If so, credit for the improvement is almost certainly to be given to the reduction in risk factors by the changes shown in Tables 4 and 5. On the other hand, mortality may be declining in the face of unchanging or rising overall morbidity because of better patient care with decreased fatality or lower recurrence rates.

In the population of Rochester, Minnesota, a major decline in stroke *morbidity* has occured from 1945 to 1974, the decrease averaging 45%, affecting both sexes and all age groups and most pronounced in the elderly (Garraway *et al*, 1979). Though no comparable data have been published on the incidence of coronary disease, these data support a decrease in morbidity by a reduction of risk factors rather than an improvement in medical care after morbidity has struck.

The Limits of Prevention

In the meantime, C-V diseases still are responsible for most deaths, the risks are still common and more must be done to control them. Before proceeding, a caveat is in order: a significant reduction in cardiovascular disease will not significantly prolong life expectancy, particularly for the years between ages 15 and 70 when productivity is greatest (Tsai *et al*, 1979). According to life table analyses of 1967-71 U.S. census and mortality data, complete elimination of cardiovascular diseases would add 12.35 years of life expectancy at birth, whereas elimination of cancer would add only 2.51 years and motor vehicle accidents, only 0.70 years (Table 6). The reason that elimination of cancer would add so little is that it mainly affects older people; thus, if most of the cancer cures involve people with only 10 years to live, and if cancer deaths are 1/6 of all deaths, then the

TABLE 6

–Added Years of Life at Birth by Reducing CVD, MN, MVA: United States, 1969–71

Causes of Death and Color/Sex Group	Per Cent of Elimination					
	10	20	30	50	70	100
Major Cardiovascular Diseases						
Total Population	0.60	1.26	1.98	3.70	6.01	12.35
White Males	0.59	1.22	1.92	3.56	5.70	11.10
White Females	0.56	1.17	1.85	3.50	5.80	12.81
Nonwhite Males	0.60	1.26	1.98	3.66	5.80	10.74
Nonwhite Females	0.76	1.59	2.51	4.72	7.69	15.66
Malignant Neoplasms						
Total Population	0.23	0.47	0.71	1.20	1.71	2.51
White Males	0.22	0.44	0.66	1.12	1.60	2.35
White Females	0.24	0.49	0.74	1.25	1.78	2.60
Nonwhite Males	0.22	0.44	0.67	1.15	1.65	2.44
Nonwhite Females	0.23	0.47	0.71	1.20	1.71	2.50
Motor Vehicle Accidents						
Total Population	0.07	0.14	0.21	0.35	0.49	0.70
White Males	0.09	0.19	0.28	0.47	0.66	0.94
White Females	0.04	0.08	0.13	0.21	0.29	0.42
Nonwhite Males	0.10	0.19	0.29	0.48	0.68	0.98
Nonwhite Females	0.04	0.07	0.11	0.19	0.26	0.38

average increase in life expectancy will be about 1/6 of 10. Obviously, if cancer equally affected all ages, life expectancy would be increased far more. Such an analyses also explains the dramatic increases in life expectancy from birth which followed conquest of acute infections of childhood.

Far more realistic than the elimination of these diseases is the likelihood that they can be reduced in frequency. But because cardiovascular diseases are so common and also affect mainly the older population, the calculated increases in life expectancy with varying degrees of reduction are less than might be expected (Table 6).

Nonetheless, considering the frequency and age of occurence of these causes of death, their elimination would add millions of productive years of life to the people of the U.S. The pain, suffering and economic costs of these diseases, even beyond their contribution to mortality, demand that attempts at prevention be increased.

How much prevention is possible? Based upon a comparison of U.S. morality rates with those in other industrialized countries, Gori and Richter provide minimal and maximal potentials of prevention for the 5 major causes of death (1973 figures) (Table 7). The minimal figures are based upon the next-to-the lowest mortality rates in other industrialized countries, the maximal upon the lowest rates now reported.

TABLE 7

Causes	Number of deaths	Percent of total mortality	Prevention potential (%)	
			Min	Max
Major cardiovascular renal diseases	1,012,341	51	39	77
Malignant neoplasms	351,055	18	25	77
Accidents--motor vehicle and other	115,821	6	38	39
Diseases of the respiratory system	92,267	5	17	38
Diabetes mellitus	38,208	2	63	74
All other causes	363,311	18		

(From Gori & Richter. Science 1978; 200:1124)

REFERENCES : *The overall status of risk factors*

Abbott MH, Abbey H, Bolling DR, Murphy EA. The familial component in longevity--a study of offspring of nonagenarians: III intrafamilial studies. Am J Med Genetics 1978; 2:105-120.

Cooper R, Stamler J, Dyer A, Garside D. The decline in mortality from coronary heart disease, USA, 1968-1975. J Chron Dis 1978; 31:709-720.

Cutler RG, Evolution of human longevity: a critical overview. Mechanisms Aging Devel 1979; 9:337-354.

Florey C, Melia RJW, Darby SC. Changing mortality from ischaemic heart disease in Great Britain 1968-76. Br Med J 1978; 1:635-637.

Garraway WM, Whisnant JP, Furlan AJ, et al. The declining incidence of stroke. N Engl J Med 1979; 300:449-452.

Gori GB, Richter BJ. Macroeconomics of disease prevention in the United States. Science 1978; 200:1124-1130.

Philippe P. Familial correlations of longevity: an isolate-based study. Am J Med Genetics 1978; 2:121-129.

Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chron Dis 1978; 31:201-306.

Soltero I, Liu K, Cooper R, et al. Trends in Mortality from cerebrovascular diseases in the United States, 1960 to 1975. Stroke 1978; 9:549-555.

Stamler J. Recent trends of major coronary risk factors and CHD mortality in the United States and other industrialized countries. In: Proceedings of National Heart, Lung, and Blood Institute Conference on Coronary Heart Disease Mortality. October 24-25, 1978. In press 1979

Sterns MP, Gaskill SP. Secular trends in ischemic heart disease and stroke mortality from 1970 to 1976 in Spanish-surnamed and other white individuals in Bexar County, Texas. Circulation 1978; 58:537-543.

Tsai SP, Lee ES, Hardy RJ. The effect of a reduction in leading causes of death: potential gains in life expectancy. Am J Public Health 1978; 68:966-971.

THE MAJOR RISK FACTORS

SMOKING

Smoking is the single most *preventable* cause of morbidity and mortality from coronary heart disease, peripheral vascular disease, chronic obstructive pulmonary disease and cancer. The fact that cigarette smokers die earlier than nonsmokers was first reported in 1938 (Pearl, 1938), corroborated in 1962 by data from Framingham (Doyle *et al*, 1962) and conclusively documented in 1964 by the monumental Hammond Report on "Smoking in Relation to Mortality and Morbidity" (Hammond, 1964*

THE SCOPE OF THE PROBLEM

As of 1976, with an estimated 60 million Americans smoking cigarettes, about 325,00 premature deaths per year were attributable to this habit, 19% to excess lung cancer deaths, 37% due to coronary heart disease (Kannel *et al*, 1978). The yearly economic cost, as of 1976, was about $27.5 billion, of which $8.2 billion were direct health care costs and $19 billion from lost earnings (Luce and Schweitzer, 1978).

The number of adult smokers in the U.S. has diminished from about 45% of the population in 1958 to about 40% as of 1974. But estimates based on questionnaires may be falsely low: 22-40% of subjects who said they had quit smoking had increased blood carboxyhemoglobin concentrations--indicating continued smoking (Sillett *et al*, 1978). Annual consumption of cigarettes has remained high despite the Surgeon General's report and everything else (Figure 8). However, the 1978 per capita consumption was the lowest in 20 years--about 9% below the peak reached in 1963. But most disturbing is the increase in smoking among teen-agers, particularly girls, which continues to rise (Figure 9) (Smoking and Health Newsletter, 1974). According to an account in the April 27, 1979 Dallas Morning News, smoking in 17 to 18-year-old boys as of 1978 has decreased from the 31% figure shown in Figure 9 to 19% but smoking among 17 to 18-year-old girls has continued to rise.

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*Hidden in the Hammond Report are some other interesting associations which have received little attention: death rates are significantly lower for non-smokers who: 1) eat fried foods 3 or 4 times a week (642) compared to those who eat no fried food (1208); 2) sleep 7 hours a night (626) compared to those who sleep more or less (2029 for those who sleep less than 5 hours, 1898 for those who sleep 10 or more hours); 3) graduate from college (676) compared to those with less education (766 for high school graduates); 4) are relatively tall (687 for 72-73 inches tall, 1065 for under 66 inches). Moreover, as subsequently reconfirmed by others, married people live longer. As Morowitz points out, "Being divorced and a nonsmoker is slightly less dangerous than smoking a pack or more a day and staying married. If a man's marriage is driving him to heavy smoking he has a delicate statistical decision to make" (Morowitz, 1975).

AGE STANDARDIZED DEATH RATES

	Nonsmokers	Cigarettes 20+ a day
Single	1,074	2,567
Married	796	1,560
Widowed	1,396	2,570
Divorced	1,420	2,675

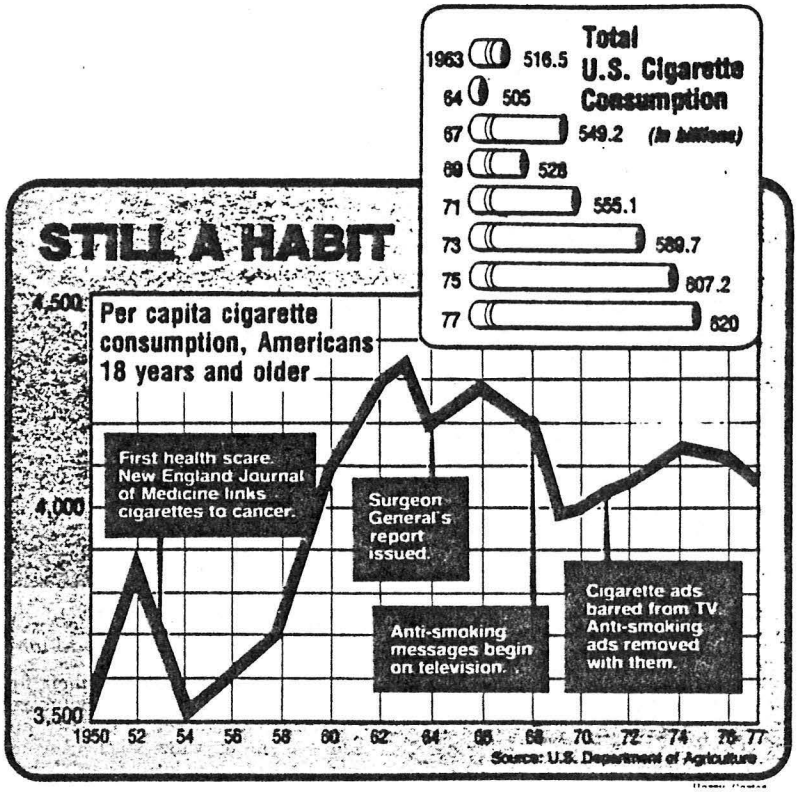


Figure 8

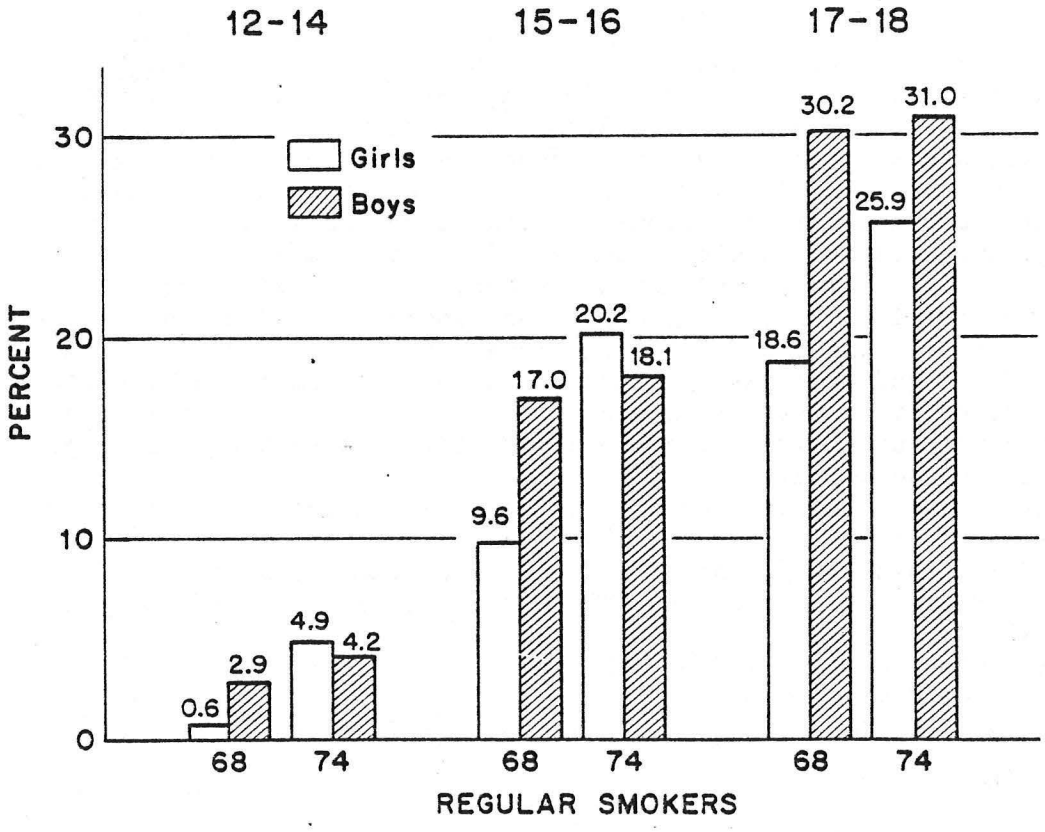


Figure 9

REFERENCES : *The major risk factors: Smoking*

Doyle JT, Dawber TR, Kannel WB. Cigarette smoking and coronary heart disease. N Engl J Med 1962; 266:796-801.

Hammond EC. Smoking in relation to mortality and morbidity. Findings in first thirty-four months of follow-up in a prospective study started in 1959. J Nat Cancer Inst 1964; 32:1161-1187.

Kannel WB, Doyle JT, Fredrickson DT, Harlan WR. American Heart Association Report of Ad Hoc Committee on Cigarette Smoking and Cardiovascular Diseases. Circulation 1978; 57:406A-407A.

Luce BR, Schweitzer SO. Smoking and alcohol abuse: a comparison of their economic consequences. N Engl J Med 1978; 298:569-571.

Morowitz HJ. Hiding in the Hammond Report. Hospital Practice 1975; pp. 35-36 (Aug).

Pearl R. Tobacco smoking and longevity. Science 1938; 87:216-217.

Sillett RW, Wilson MB, Malcolm RE, Ball KP. Deception among smokers. Br Med J 1978; 2:1185-1186.

THE RISKS OF SMOKING

The data concerning overall and specific disease mortality and morbidity are easiest found in the two up-dated publications of the Public Health Service, the 1976 Health Consequences of Smoking (HEW Publication No. CDC-78-8357) and the 1979 Surgeon General's Report on Smoking, released on January 11, 1979, and soon to be available from the Government Printing Office. These two publications summarize virtually all of the known data on the risks of smoking, but since they are so voluminous and often unavailable, some of the more recent and more accessible evidence will be reviewed.

Overall mortality: Among 4004 men and women, 35 to 54 years of age, who were followed for 11 years, the smoker to nonsmoker age-adjusted mortality ration was 2.1 for all causes and 3.6 for coronary heart disease (Friedman *et al*, 1979). The significant association could not be eliminated by accounting for 48 other possible characteristics, individually and in combination, making it exceedingly unlikely that any other factor than smoking was responsible for the increased mortality.

Similar doubling of overall death rates have been noted among smokers in these populations:

-the 5,127 Framingham residents followed for 22 years (Kannel, 1977).
-3,686 San Francisco longshoremen followed for 22 years (Paffenbarger *et al*, 1978)
-18,786 Scottish people, randomly chosen, followed for 12 years (Hawthorne and Fry, 1978)
-34,440 male physicians in Britain followed for 20 years (Doll and Peto, 1976)

Coronary heart disease: Though the relative risk of smoking is greatest for cancer of the lung, the absolute risk is far greater for coronary disease. The chances of an American smoker dying of lung cancer are about 10 times greater than a nonsmoker; the chances of dying of coronary disease are about 2-4 times greater. But the number of smoking-related cancer deaths per year in the U.S. is about 70,000; whereas, the number of smoking-related cardiovascular deaths per year is about 250,000.

As to morbidity, in Framingham the increase in risk for coronary events was particularly noted in younger men, less obvious in men over age 50, and was not seen in women at any age. Others, however, have shown that women who smoke, even those who are below age 50, have a much greater risk of myocardial infarction, some 20-fold higher for those who smoke 35 or more cigarettes per day (Slone *et al*, 1978) (Figure 10). They also have a greater chance for sudden death (Spain *et al*, 1973). The risk for premature coronary disease is particularly enhanced by concomitant use of estrogen-containing oral contraceptives (Mann *et al*, 1976).

The risk of coronary disease from smoking is clearly independent from (though additive to) that of other known risk factors such as hypertension or hypercholesterolemia (Reid *et al*, 1976).

Smokers who survive a myocardial infarction and quit smoking have a 62% reduction in mortality over 6 years even though their recurrence rate for myocardial infarction was not reduced (Sparrow *et al*, 1978). Clearly, smoking increases mortality in people having coronary disease as well as likely being a factor for the development of coronary atherosclerosis (Matroos *et al*, 1979).

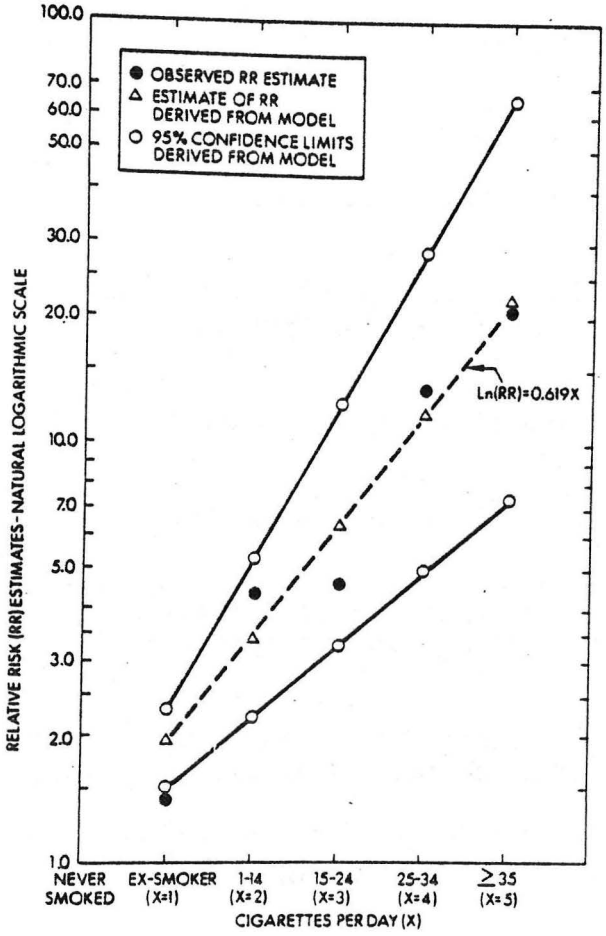


Figure 10

The associations of smoking with cardiovascular disease have usually been made after death or serious disease has occurred. An interesting study of the association at an earlier phase was done among 2014 presumably healthy Norwegian men, aged 40 to 49, who had no signs or symptoms of coronary disease, hypertension, or diabetes (Erikssen and Enger, 1978a). Based on a questionnaire, resting and exercise-ECGS, 115 were diagnosed as having "latent" coronary heart disease. Coronary angiography was done in 109 or these 115 men and was positive in 69 of the 109. The extent of coronary atherosclerosis was directly related to the number of cigarettes smoked and the association was independent of other risk factors (Erikssen and Enger, 1978b).

Other atherosclerotic diseases:

Stroke: the risk is less than for coronary disease: the relative risk for all strokes is around 1.5 for smokers (Surgeon General's Report, 1979), but was found to be close to 4 for subarachnoid hemorrhage both in men and women smokers (Bell and Symon, 1979). In another study of women, the risk of subarachnoid hemorrhage was 5.7 times increased among smokers and was

22 times among smokers taking oral contraceptives (Petitti and Wingerd, 1978).

Peripheral vascular disease (PVD): Here the association in both men and women is very strong, with about 80% of patients having atherosclerotic peripheral vascular disease being smokers. Smoking acts synergistically with diabetes, so that a diabetic who smokes has a 50% greater risk of PVD. The risk of PVD relates to the number of cigarettes smoked and the blood CO-Hb (Wald *et al*, 1973).

Aortic aneurysms: Once again, the association is very strong with a dose-dependent mortality ratio of 4-5 in men who smoke one pack per day and a ratio of 7-8 in smokers of two ppd (Health Consequences of Smoking, 1976).

Thromboangiitis Obliterans (Buerger's Disease): This vasculitis is almost exclusively seen in smokers.

Hypertension: Even though nicotine and smoking raise the blood pressure acutely, hypertension does not seem to be more prevalent among smokers. In fact, smokers, on the average, may have slightly lower blood pressures; and their pressures may go up if they quit smoking (Seltzer, 1974), though others find no change on quitting (Greene *et al*, 1977; Gordon *et al*, 1975).

There's probably a logical explanation for this reverse relationship: smokers are about 10 to 12 pounds lighter than nonsmokers of the same sex, age, and height (Khosla and Lowe, 1972). When they stop smoking, body weight increases from 4 to 30 pounds (Fletcher and Doll, 1969; Blitzer *et al*, 1977). The differences in blood pressure likely reflect the differences in weight, rising with the weight gain.

On the other hand, deaths from hypertension are more common among smokers (Doll and Peto, 1976) and two groups have observed a definite (5-fold) greater incidence of malignant hypertension among smoking hypertensives than among nonsmoking hypertensives (Isles *et al*, 1979; Bloxham *et al*, 1979).

REFERENCES : *The risks of smoking*

Bell BA, Symon L. Smoking and subarachnoid haemorrhage. Br Med J 1979; 1:577-578.

Blitzer PH, Rimm AA, Gieger EE. The effect of cessation of smoking on body weight in 57,032 women: cross-sectional and longitudinal analyses. J Chron Dis 1977; 30:415-429.

Bloxham CA, Beevers DG, Walker JM. Malignant hypertension and cigarette smoking. Br Med J 1979; 1:581-583.

Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976; 2:1525-1536.

Erikssen J, Enger SC. Smoking, lung function, physical performance and latent coronary heart disease in presumably healthy middle-aged men. Acta Med Scand 1978; 203:509-516. (a)

Erikssen J, Enger SC. The effect of smoking on selected coronary heart disease risk factors in middle-aged men. Acta Med Scand 1978; 203:27-30. (b)

Fletcher C, Doll R. A survey of doctors' attitudes to smoking. Br J Prev Soc Med 1969; 23:145-153.

Friedman GD, Dales LG, Ury HK. Mortality in middle-aged smokers and nonsmokers. N Engl J Med 1979; 300:213-217.

Gordon T, Kannel WB, Dawber TR, McGee D. Changes associated with quitting cigarette smoking: the Framingham study. Am Heart J 1975; 90:322-328.

Green SB, Aavedal MJ, Tyroler HA, et al. Smoking habits and blood pressure change: a seven year follow-up. J Chron Dis 1977; 30:401-413.

Hawthorne VM, Fry JS. Smoking and health: the association between smoking behavior, total mortality, and cardiorespiratory disease in west central Scotland. J Epidem Commun Health 1978; 32:260-266.

Isles C, Brown JJ, Cumming AMM, Lever AF, et al. Excess smoking in malignant-phase hypertension. Br Med J 1979; 1:579-581.

Kannel WB. Preventive cardiology: what should the clinician be doing about it? Postgrad Med 1977; 61:74-85.

Khosla T, Lowe CR. Obesity and smoking habits by social class. Br J Prev Soc Med 1972; 26:249-256.

Mann JI, Doll R, Thorogood M, Vessey MP, Waters WE. Risk factors for myocardial infarction in young women. Br J Prev Soc Med 1976; 30:94-100.

Matroos A, Magnus K, Strackee J. Fatal and nonfatal coronary attacks in relation to smoking in some dutch communities. Am J Epidemio 1979; 109:145-151.

Paffenbarger RS Jr., Brand RJ, Sholtz RI, Jung DL. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. Am J Epidem 1978; 108:12.

Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. Lancet 1978; 2:234-235.

Reid DD, Hamilton PJS, McCartney P, Rose G, et al. Smoking and other risk factors for coronary heart-disease in British civil servants. Lancet 1976; 2:979-984.

Seltzer CC. Effect of smoking on blood pressure. Am Heart J 1974; 87:558-564.

Slone D, Shapiro S, Rosenberg L, et al. Relation of cigarette smoking to myocardial infarction in young women. N Engl J Med 1978; 298:1273-1276.

Spain DM, Siegel H, Bradess VA. Women smokers and sudden death. JAMA 1973; 224:1005-1007.

Sparrow D, Dawber TR, Colton T. The influence of cigarette smoking on prognosis after a first myocardial infarction. J Chron Dis 1978; 31:425-432.

THE EFFECTS OF SMOKING CESSATION ON CARDIOVASCULAR DISEASE

People who quit smoking progressively lose their excess cardiovascular risk. In Framingham, a decrease in coronary attacks was evident within 2 years (Kannel, 1978). Over 18 years, men aged 45-64 who quit had less than half the risk for coronary events than those who continued to smoke (Figure 11) (Gordon *et al*, 1974). Among those over age 65, the risk was unchanged; presumably those smokers who survive until age 65 are the select few, tough enough to withstand all of the hazards.

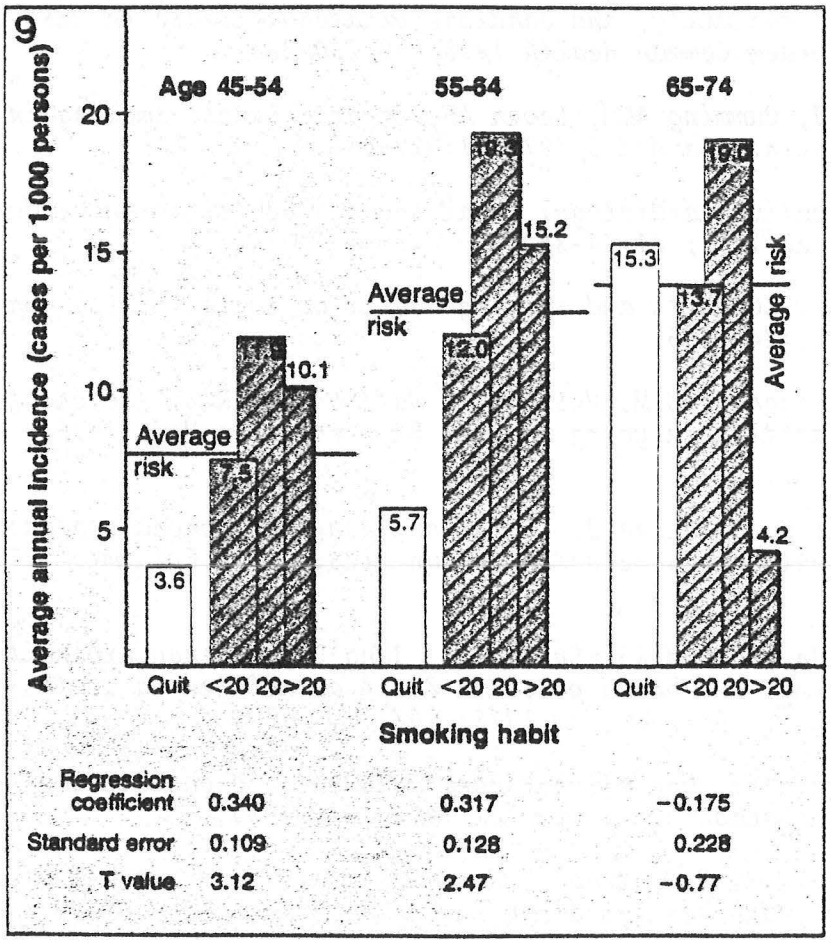


Figure 11

One of the better demonstrations of the lesser mortality among people who quit is the study of British physicians (Doll and Peto, 1976). Having shown that between a half and a third of all cigarette smokers will die because of their smoking, the authors compared the mortality from various diseases over the ensuing 15 years among those who quit to those who continued smoking (Table 8) and to those who were life-long nonsmokers (Table 9). It is obvious that mortality was generally lower by 5 years after stopping but didn't fall to that of life-long nonsmokers even after 15 years.

TABLE 8

—Mortality in ex-cigarette smokers by number of years they had stopped smoking compared with mortality in continuing cigarette smokers

Cause of death	No of deaths as % of No expected in continuing cigarette smokers (actual No in parentheses) Years since smoking stopped:			
	<5	5-9	10-14	15
Cancer of lung	102 (15)	35 (12)	28†(9)	11 (7)
Cancer of oesophagus and other respiratory sites	45 (4)		17 (3)	
Chronic bronchitis and emphysema and pulmonary heart disease	112 (9)	158 (30)	22 (4)	28 (12)
Other conditions closely associated with smoking	145 (7)	44 (5)	49 (5)	49 (10)
Ischaemic heart disease in men 30-54 years	54 (7)	35 (10)	45 (10)	47 (7)
Ischaemic heart disease in men 55-64 years	111 (19)	83 (34)	102 (38)	74 (45)
Ischaemic heart disease in men 65 years and over	76 (24)	102 (76)	87 (62)	83 (148)
Myocardial degeneration	31 (3)	87 (21)	76 (19)	47 (31)
Other conditions associated with smoking	72 (26)	79 (67)	84 (65)	71 (118)
All other conditions	102 (55)	100 (125)	84 (97)	86 (210)
All causes at 30-64 years	86 (67)	80 (141)	69 (104)	56 (106)
All causes at 65 and over	87 (99)	89 (242)	78 (206)	71 (484)
All causes	87 (166)	85 (383)	75 (310)	68 (590)
Mean No of years stopped	3·3	7·5	12·4	21·6

TABLE 9

—Mortality in ex-cigarette smokers by number of years stopped smoking compared with mortality in lifelong non-smokers. Current smokers are described as having stopped 0 years ago

Cause of death	No of deaths divided by number expected in lifelong non-smokers Years since smoking stopped:					No of deaths in lifelong non-smokers
	0	<5	5-9	10-14	>15	
Cancer of lung	15·8	16·0	5·9	5·3†	2·0	7
Cancer of oesophagus and other respiratory sites	6·1	2·9		1·2		3
Chronic bronchitis and emphysema and pulmonary heart disease	35·6	34·2	47·7	7·3	8·1	2
Other conditions closely associated with smoking	7·7	10·2	3·2	3·4	3·2	5
Ischaemic heart disease in men 30-54 years	3·5	1·9	1·3	1·4	1·3	32
Ischaemic heart disease in men 55-64 years	1·7	1·9	1·4	1·7	1·3	75
Ischaemic heart disease in men 65 years and over	1·3	1·0	1·3	1·2	1·1	182
Myocardial degeneration	2·4	0·7	2·1	1·8	1·0	47
Other conditions associated with smoking	1·8	1·2	1·3	1·4	1·1	194
All other conditions	1·2	1·2	1·2	1·0	1·0	390
All causes at 30-64 years	2·0	1·7	1·6	1·4	1·1	326
All causes at 65 and over	1·6	1·4	1·4	1·2	1·1	611
All causes	1·8	1·5	1·5	1·3	1·1	937

REFERENCES: *The effects of smoking cessation on cardiovascular disease*

Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976; 2:1525-36.

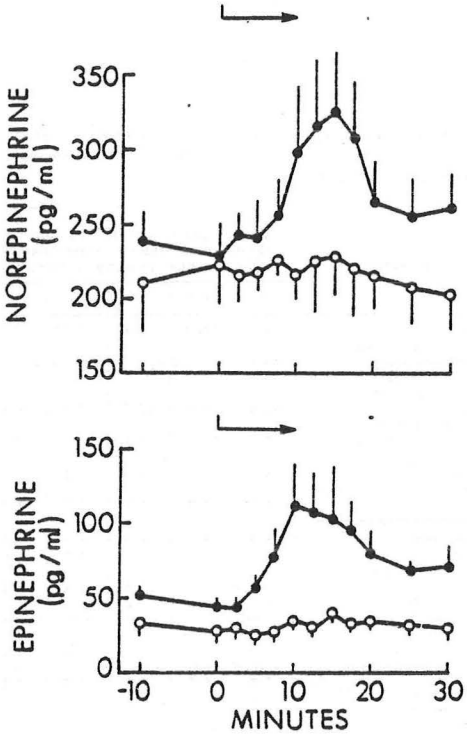
Gordon T, Kannel WB, McGee D. Death and coronary attacks in men after giving up cigarette smoking. Lancet 1974; 2:1345-1348.

Kannel WB. Hypertension, blood lipids, and cigarette smoking as co-risk factors for coronary heart disease. NY Acad Sciences 1978; 128-139.

THE MECHANISMS BY WHICH SMOKING CAUSES CARDIOVASCULAR DISEASE:

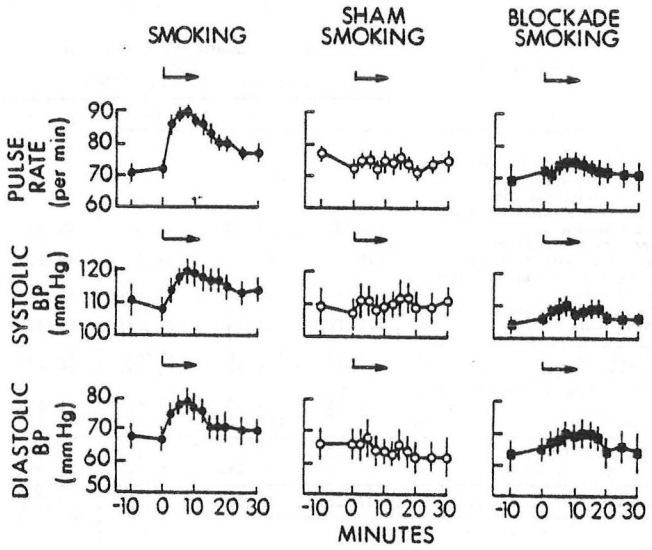
Two main effects of smoking are likely responsible: 1) the effect of nicotine, likely mediated via the sympathetic nervous system and 2) the desaturation of hemoglobin by CO. Other factors may be involved, including an increase in platelet adhesiveness (Levine, 1973). Some believe that all of the deleterious effects arise from pulmonary dysfunction (Cohen, 1978).

Smoking invokes rapid rises in heart rate and blood pressure, which are related to significant increases in plasma catecholamines and which are prevented by adrenergic blockade (Figures 12 & 13) (Cryer *et al*, 1976). These effects occurred after 2 cigarettes were smoked over a 10-minute interval by a group of habitual smokers. Lesser hemodynamic effects follow smoking low-nicotine cigarettes (Tachmes, *et al*, 1978).



Mean (±S.E.) Plasma Norepinephrine and Epinephrine Concentrations in Association with Smoking (Closed Symbols) and with Sham Smoking (Open Symbols). The arrows indicate the period of smoking (or sham smoking).

Figure 12



Mean (±S.E.) Pulse Rates, Systolic Blood Pressures and Diastolic Blood Pressures during Smoking (Left, Closed Circles), Sham Smoking (Center, Open Circles) and Smoking during Adrenergic Blockade (Right, Closed Squares). The arrows indicate the periods of smoking (or sham smoking).

Figure 13

Cigarette smoke contains CO, which because of its great affinity for hemoglobin, converts from 5 to 10% to carboxyhemoglobin in the habitual smoker. The decrease in oxygen carrying capacity of the blood could obviously induce tissue damage, particularly in those with extensive atherosclerosis. Carboxyhemoglobin levels were found to provide a better indication of cardiovascular risk than the smoking history: a carboxyhemoglobin level of 5% or more was associated with 21 times more C-V disease than a carboxyhemoglobin level below 3% in people of the same age, sex, smoking history and current smoking habits (Wald *et al*, 1973). More, not less, CO is inhaled in filtered cigarettes: smoke passing through a cigarette is diluted by air entering through the porous cigarette paper; since the paper surrounding the filter is relatively non-porous, the CO content of the smoke passing through this type of cigarette is about 25% higher (Wald, 1976). This may explain the British findings of lesser lung cancer but more ischemic heart disease with the wider use of presumably safer cigarettes (Wald, 1976). Filters with perforations should not have increased CO in the smoke.

In patients with angina, exposure to other people's cigarette smoke (i.e., passive smoking) may decrease exercise tolerance and precipitate anginal attacks (Aronow, 1978). Long-term hazards of passive smoking have not been reported.

Special risks in women: Pregnant women who smoke expose their fetuses to multiple risks including lower birth weights, shorter gestation, higher rates of spontaneous abortion, and higher perinatal mortality (Population Reports, 1979). Moreover, the umbilical and placental vessels of smoking mothers show marked vascular changes, thereby conceiviably branding the infant with a greater propensity toward eventual cardiovascular disease (Asmussen, 1978).

Women who smoke have an earlier menopause (Jick *et al*, 1977) and this might explain part of the increased coronary disease noted among women with early menopause.

REFERENCES: *Mechanisms by which smoking causes cardiovascular disease*

Aronow WS. Effect of passive smoking on angina pectoris. N Engl J Med 1978; 299:21-24.

Asmussen I. Arterial changes in infants of smoking mothers. Postgrad Med J 1978; 54:200-204.

Cohen BH. Is pulmonary dysfunction the common denominator for the multiple effects of cigarette smoking? Lancet 1978; 2:1024-1027.

Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976; 295:573-575.

Jick H, Porter J, Morrison AS. Relation between smoking and age of natural menopause. Lancet 1977; 1:1354-1355.

Levine PH. An acute effect of cigarette smoking on platelet function. Circulation 1973; 48:619-623.

Population Reports. Tobacco--hazards to health and human reproduction. Series L, #1, 1979.

Tachmes L, Fernandez RJ, Sackner MA. Hemodynamic effects of smoking cigarettes of high and low nicotine content. Chest 1978; 74:243-246.

Wald N, Howard S, Smith PG, Kjeldsen K. Association between atherosclerotic diseases and carboxyhaemoglobin levels in tobacco smokers. Br Med J 1973; 1:761-765.

Wald N. Mortality from lung cancer and coronary heart-disease in relation to changes in smoking habits. Lancet 1976; 1:136-138.

Recognizing the multiple risks of smoking and the benefits of not smoking, let's examine ways to prevent or rescue people from this nefarious habit.

PREVENTION OF SMOKING

People start smoking for social reasons but many become addicted and have great difficulty stopping. More and more young people are starting to smoke.* Prevention is obviously important but neither the reasons why people start nor the reasons they continue to smoke are known for certain.

The onset of smoking: School children who begin smoking are more likely to also consume alcohol and use illicit drugs (Block and Goodman, 1978). They usually start smoking because of peer pressures to appear more mature, with enticements from their smoking parents and the media. Most are aware of the long-term dangers of smoking when they start (Evans *et al*, 1978). But of those who smoke more than a single cigarette, only 15% avoid becoming regular, dependent smokers (McKennell and Thomas, 1967). And though most of them will soon wish to quit, only about one-quarter can, so that once a teenager starts, it's 2 chances out of 3 that he or she will be hooked for life.

The addiction to smoking: Cigarettes are far more addicting than alcohol or barbiturates. Only about 2% of smokers can use them intermittently, whereas most who drink alcohol or take sleeping pills can use them or do without. With alcohol use, only a small minority become dependent; with smoking, only a small minority avoid dependence. Dependence on alcohol or barbiturates usually develops in a setting of psychological or social difficulty, whereas the most well-adjusted person who starts to smoke will likely become addicted.

After smoking is started for psychosocial reasons, the pharmacological effects of nicotine produce dependence and addiction (Russell, 1974). With each puff, 50 to 150 µg of nicotine are absorbed through the oral mucosa and alveoli, about 1 to 2 mg per cigarette. Nicotine is what the smoker craves and this can be satisfied by nicotine injection or nicotine-containing chewing gum (Russell *et al*, 1976). When switched to low-nicotine cigarettes (Turner *et al*, 1974) or given ventilated holders which dilute the smoke (Sutton *et al*, 1978), they compensate at least partially by increasing the intake from each cigarette or smoking more cigarettes.

According to Russell, "There is no evidence whatsoever that other components of tobacco smoke...are intrinsically rewarding. If it were not for the nicotine in tobacco smoke, people would be little more inclined to smoke cigarettes than they are to blow bubbles or light sparklers" (Russell, 1974).

Nicotine has multiple actions within the brain and which ones are responsible for dependency and addiction are not known. Apparently, the smoker needs a nicotine boost every 20 to 30 minutes through the waking hours.

Most nicotine is absorbed, extremely rapidly, from the alveoli. Absorption from the mouth is slower and less likely to produce dependence. Buccal absorption is pH dependent; little nicotine is absorbed in the mouth from the acidic smoke (about pH 5.5) of the flue-cured tobacco used in most cigarettes; more is absorbed from the alkaline smoke (about 8.5) of the air-cured tobaccos

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*In an April 26 speech, reported in the April 27, 1979 Dallas Morning News, HEW Secretary Califano stated that 1978 surveys show a continued rise to over 26% in 17 to 18-year-old girls who smoke but a decline among 17 to 18-year-old boys to 19%. Of 12 to 18-year-olds, 3.3 million are regular smokers.

used in pipes and cigars. Thus, it is possible to get a nicotine effect from pipes and cigars without inhaling them, but with less chance for dependence. However, some pipe and cigar smokers, particularly those who have switched from cigarettes, continue to inhale so they are as likely to remain dependent and to suffer the ill effects (Cowie *et al*, 1973).

Attempts to stop children from starting: Very little work has been done where it would likely do the most good. Evans *et al* in Houston have shown that they could, at least temporarily, deter about half of seventh-grade children who had smoked at least one cigarette within the previous month from continuing to smoke by the use of short videotapes emphasizing the short and long-term benefits of not smoking and explaining peer pressure and its effects on smoking behavior (Evans *et al*, 1978).

Some broader remedies that may reduce the number of people who take up smoking include:

1. Raise the cost by increasing taxes on cigarettes: shown to be effective (Peto, 1974), but hardest on the poor, who smoke the most. Interestingly, the cost of cigarettes has risen less than the Consumer Price Index over the past 20 years. In England, a supplementary tax has been levied on all cigarettes with 20 mg or more tar. As a result, their share of the market, which has been stable for the preceeding year, fell from 15% to 3% in 3 months (Editorial, *Lancet* 1979).

2. Restrict advertising, particularly the seductive (use of athletic, attractive models) and misleading (association with the good-life, sponsorship of athletic competitions) which induce children to take up smoking.

3. Increase public awareness of the dangers: only 28% of adults named cigarette smoking as a probable cause of heart attacks (Shekelle and Lin, 1978). Public education works: the broadcasting of antismoking commercials in 1968-70 reduced cigarette consumption in the U.S. by 14% per year (Atkinson and Townsend, 1977). Health professionals should set an example by not smoking and should repeatedly warn their patients of the dangers and assist them in quitting.

4. Make it more difficult for children to buy cigarettes, enforcing restrictions as with the sale of alcohol.

5. Ensure the rights of non-smokers to clean air by prohibiting smoking in all enclosed places where people work and play.

6. Provide inexpensive, accessible smoking cessation programs: Since each smoker costs society at least $460 per year (as of 1976), society should assume more of the cost of cessation. These programs work well enough to be used: 25% of those who participate are abstinent after a year (Hunt and Matarazzo, 1973) and some programs may do better.

7. Stop governmental support of the tobacco industry: The industry should be required to decrease the content of harmful ingredients.

8. Encourage those who cannot quit to reduce their risk by smoking fewer cigarettes, using low tar brands with filters, inhaling less, and smoking less of each cigarette.

Cessation of smoking: About 30 million Americans have stopped since 1964, but most of them were probably fairly light smokers. Many more would like to quit but haven't. However, anti-smoking efforts have probably been more effective than they appear since, without them, there would likely have been the progressive increase in smoking that had been seen before they were begun. Instead of a per capita consumption of around 4,200 per year, the number would likely be around 5,400 (Warner, 1977).

Individual physicians, by talking to patients, can be effective in getting them to stop. British Civil Servants, aged 40-59 who were identified as being at relatively high risk, were given 15 minute talks, 3 to 5 over 6 months, which presented the facts, encouraged the smoker to quit, and offered advice concerning various techniques and problems of stopping (Rose and Hamilton, 1978). This group was compared to another group who were identified as being at risk but then left alone. A significant reduction in the number of smokers and number of cigarettes smoked was accomplished (Table 10).

TABLE 10

Smoking status after one and three years

	One year		*Three years*	
	Intervention	*Normal care*	*Intervention*	*Normal care*
No. completing questionnaire	577 (81%)	626 (86%)	456*(64%)	511 (70%)
Non-smokers	227 } 363	56 } 75	162 } 260	74 } 100
Pipe/cigars only	136 }	19 }	98 }	26 }
'Cigarettes reduced 50% +'	83	23	42	17
Reduction nil or <50%	131	528	150	394
Mean cigarettes/day (all attendants)	'4·8'	'16·6'	'6·2'	'15·7'

*Smoking data incomplete in four.

The National Cancer Institute will provide individual practitioners a "Helping Smokers Quit" kit containing a physicians guide and 50 copies of pamphlets and posters. They can be obtained, at no cost, by writing the National Institute of Health, Bldg 31, Room 4B39, Bethesda MD 20014.

The following additional techniques have been tried (*Medical Letter* 1978; 20:107):

1. Fear: this can backfire since some will smoke more to relieve their anxiety (Leventhal, 1971).

2. Drugs: Lobeline has many of the same pharmacological effects as nicotine but it has not been found to be better than a placebo. Use of nicotine chewing gum allowed 10 of 43 to remain abstinent after one year (Russell *et al*, 1976). Tranquilizers have not been shown to help.

3. Filters: The Water Pik system uses 4 filters, each to be used for 2 weeks, to gradually reduce about 90% of the nicotine, etc., so that in 8 weeks the smoker can simply quit. Additional filters are available (2 for $5) for those who can't. It would be a lot cheaper just to choose low-tar, low-nicotine cigarettes.

4. Adversive Conditioning: Following the report of Lichtenstein *et al* (1973), the rapid smoking method, wherein the smoker inhales every 6 seconds until dizzy or nauseated, has been widely used. It's avail-

able for $495 at the Schick Treatment Centers. Claims for success are as high as 85% in 6 months but it can produce marked tachycardia and ECG changes (Lichtenstein and Glasgow, 1977).

5. Group Programs: The Seventh-Day Adventists sponsor a Five-Day Plan with lectures and group meetings. SmokeEnders have 8 weekly meetings with a highly structured program emphasizing behavior modification, positive conditioning, and periodic reunions for a year. The cost is $295. With such programs, about 80% will quit smoking temporarily but only 20 to 25% remain abstinent after a year (Kanzler *et al*, 1976).

6. Self-Help Programs: A multitude of books, pamphlets, and guides are available. Most probably are of limited value. Some use aversion techniques such as wearing a large rubber band on the wrist and snapping it smartly so that it hurts whenever the urge to smoke returns (Nelson, 1977). Most use behavioral modification and various conditioning approaches. Thereby as many as 70% may remain abstinent after 6 months (Lando, 1977).

7. Cold Turkey: Personal experience documents its effectiveness: Even after 24 years of 2-3 ppd, it is possible to quit (as of now). This may be best since "For some people, the process of reduction and all the various aids may serve only to focus more attention on what they're missing" (*Medical Letter* 1978; 20:107).

Making smoking safer: Recognizing that most can't (or won't) quit, efforts have been made to reduce the risk of continued smoking. They work, at least as far as reducing the histologic changes in the bronchial epithelium (Basal-cell hyperplasia, loss of cilia, occurrence of cells with atypical nuclei) which are thought to lead to cancer and COPD (Auerbach *et al*, 1979). In men dying in 1955-60 who smoked 20-39 cigarettes a day, such changes were found in 13.2%; in men dying in 1970-1977 who smoked the same number of cigarettes, these changes were found in only 0.8%.

Whether these same changes have reduced the cardiovascular risks is less certain: cigarettes with non-perforated filters deliver more carbon monoxide (CO) than do plain cigarettes (Wald 1976) and CO may be the major culprit in causing cardiovascular disease. Obviously, the monitoring of smoke needs to include CO, as well as nitrous oxides, hydrogen cyanide, and acrolein, all of which may be toxic.

The changes that have been made to make cigarettes safer include:

1. *Switching to filtered cigarettes:* This is likely the most effective step taken. First introduced in 1954, they have progressively taken over more and more of the market, with no deliberate attempt to induce people to switch. Obviously, the message became apparent and the tobacco companies were happy to meet (and increase) the demand.

2. *Switch to low-tar, low-nicotine cigarettes:* Since publication of the first Surgeon General's report in 1964, significant reduction in the tar and nicotine content of cigarettes has been accomplished by various manipulations (in addition to the use of filters) including the use of more porous paper, the use of milder tobacco which is reblended or put through extraction processes, addition of filters and materials which slow down the burning rate. As a result, most brands now sold

have much less of the "toxic" elements found in the typical pre-1960 cigarette: 43 mg of tar, 3.0 mg of nicotine, 270 µg of NO, 410 µg of HCN, and 130 µg of acrolein (Gori and Lynch, 1978).

As noted before, the reduction in nicotine may be counter-productive since it takes a certain level to satisfy the smoker's dependency. The best cigarette might be one that is low in tar and medium high in nicotine. Russell believes a 6 mg tar, 1 mg nicotine cigarette should be feasible (Russel, 1976).

Smokers apparently can adapt to lesser amounts of nicotine and may not increase their total smoking to compensate totally for less nicotine per cigarette. With cigarettes having progressively lower tar and nicotine content, smokers smoked more cigarettes and each further down, but still had a fall in CO-hemoglobin levels to about half of where they started (Turner *et al*, 1974).

A few months ago, the director of the Division of Cancer Cause and Prevention at the National Cancer Institute, Dr. Gio Gori, incited a great deal of criticism by publishing a paper which said that "a smoker can consume (a variable number of currently available cigarettes) daily without increasing his mortality risk substantially above that of a nonsmoker" (Gori and Lunch, 1978). This statement is based upon the assumption that the risks are directly related to the numbers of cigarettes (and the amounts of their toxic products), with an average "critical level of pre-1960 cigarette consumption of 5.7 for lung cancer, 4.2 for coronary artery disease, 10.0 for COPD, and 2.0 for all causes of disease." Thus, one could "safely" smoke daily the equivalent of 2 pre-1960 cigarettes which would equal these number of cigarettes available in 1978:

Carlton Menthol	- 23
Now Menthol	- 18
Now	- 17
Stride	- 17
Carlton	- 16

The numbers that are supposedly safe are considerably lower (less than 10 a day) for some, including True, Decade, Kent Golden Lights, L & M Lights, and Pall Mall Extra Mild. And for others, fewer than 5 a day are "safe," including Benson & Hedges Light, Merit, Newport Lights Menthol, and Tempo.

As with radioactivity, there is likely no "safe" level of smoking but Gori and Lynch's analysis may be helpful in showing smokers how to reduce their risk if they can't quit.

3. *Adopt safer smoking habits* such as: inhale less, smoke less of each cigarette, take fewer puffs from each cigarette, take the cigarette out of the mouth between puffs.

4. *Switch to pipes or large cigars* but don't inhale their smoke. If the amoung of nicotine absorbed through the buccal mucosa is enough to satisfy the dependency, but not in itself harmful, the addicted smoker may be able to significantly reduce his risk by reducing his intake of tar, CO and other toxic inhalants.

REFERENCES: Prevention of smoking

Atkinson AB, Townsend JL. Aconomic aspects of reduced smoking. Lancet 1977; 2:492-495.

Auerbach O, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking, 1955-1960 vs 1970-1977. N Engl J Med 1979; 300:381-386.

Block JR, Goodman N. Illicit drug use and consumption of alcohol, tobacco, and over-the-counter medicine among adolescents. Intl J Addictions 1978; 13:933-946.

Cowie J, Sillett RW, Ball KP. Carbon-monoxide absorption by cigarette smokers who change to smoking cigars. Lancet 1973; 1:1033-1035.

Editorial. Silent Prevention. Lancet 1979; 1:705.

Evans RI, Mozelle RM, Mittelmark MB, Hansen WB, Bane AL, Havis J. Deterring the onset of smoking in children: knowledge of immediate physiological effects and coping with peer pressure, media pressure and parent modeling. J Appl Social Psychol 1978; 8:126-135.

Gori GB, Lynch CJ. Toward less hazardous cigarettes. JAMA 1978; 240:1255-1259.

Hunt WA, Matarazzo JD. Three years later: recent developments in the experimental modification of smoking behavior. J Abnormal Psychol 1973; 81:107-114.

Kanzler M, Jaffe JH, Zeidenberg P. Long- and short-term effectiveness of a large-scale proprietary smoking cessation program --a 4-year follow-up of smokenders participants. J Clin Psychol 1976; 32:661-669.

Lando HA. Successful treatment of smokers with a broad-spectrum behavioral approach. J Consult Clin Psychol 1977; 45:361-366.

Leventhal H.. Fear appeals and persuasion: the differentiation of a motivational construct. Am J Public Health 1971; 61:1208-1224.

Lichtenstein E, Harris DE, Birchler GR, Wahl JM, Schmahl DP. Comparison of rapid smoking, warm, smoky air, and attention placebo in the modification of smoking behavior. J Consult Clin Psychol 1973; 40:92-98.

Lichtenstein E, Glasgow RE. Rapid smoking: side effects and safeguards. J Consult Clin Psychol 1977; 45:815-821.

Luepker RV, Hurd P, Pechacek T et al. Prevention of cigarette smoking in 7th grade school children. Circulation 1978; 57 & 58(Suppl II):94 (Abstract).

McKennell AC, Thomas RK. Adults and adolescents' smoking habits and attitudes. H.M. Stationery Office, 1967.

Medical Letter: Aids for patients who want to stop smoking. Med Letter 1978; 20:107-108.

Nelson SK. Behavioral control of smoking with combined procedures. Pschol Reports 1977; 40:191-196.

Peto J. Price and consumption of cigarettes: a case for intervention? Br J Prev Soc Med 1974; 28:241-245.

Rose G, Hamilton PJS. A randomised controlled trial of the effect on midale-aged men of advice to stop smoking. J Epidemol Community Health 1978; 32:275-281.

Russell MAH. Realistic goals for smoking and health: a case for safer smoking. Lancet 1974; 2:254-258.

Russell MAH. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. Br Med J 1976; 1:1430-1433.

Russell MAH, Wilson C, Feyerabend C, Cole PV. Effect of nicotine chewing gum on smoking behaviour and as an aid to cigarette withdrawal. Br Med J 1976; 2:391-393.

Shekelle RB, Liu SC. Public beliefs about causes and prevention of heart attacks. JAMA 1978; 240:756-758.

Sutton SR, Feyerabend C, Cole PV et al. Adjustment of smokers to dilution of tobacco smoke by ventilated cigarette holders. Clin Pharmacol Ther 1978; 24:395.

Turner JA McM, Sillett RW, Ball KP. Some effects of changing to low-tar and low-nicotine cigarettes. Lancet 1974; 2:737-740.

Wald N. Mortality from lung cancer and coronary heart-disease in relation to changes in smoking habits. Lancet 1976; 1:136-138.

Warner KE. The effects of the anti-smoking campaign on cigarette consumption. Am J Public Health 1977; 67:645-650.

HYPERTENSION

THE PREVALENCE OF HYPERTENSION

Of all the identified risk factors for CV disease, hypertension has the largest impact, both because it is so prevalent and because it is so damaging. The prevalence of casual blood pressures above 160/95 in a large, representative sample of the U.S. population in the National Health and Nutrition Survey of 1971-74 is shown in Figure 14. The prevalence rises with age after childhood. Recent surveys find as much or more hypertension among Spanish-speaking (Schreiber *et al*, 1979) and American Indian (Goldman *et al*, 1979) populations.

What should be called "hypertension"? The official level of 160/95 is too high for young men since a greater than 50% increase in mortality is seen for levels above 140/90, if left untreated, in men below age 40 (Kaplan, 1978).

As George Pickering has long emphasized, blood pressures are extremely variable, and there is no distinct separation at any sphygmomanometer reading between normotension and hypertension (Pickering, 1972). On the other hand, there is a step-wise increase in CV morbidity and mortality with diastolic levels above 90 mm Hg and that likely is the appropriate level to be considered abnormally high for all people (Kannel, 1977).

The frequency distribution for diastolic pressures shows that the prevalence of what is called "hypertension" will obviously differ markedly with the level that is chosen (Figure 15).

As to systolic levels, the progressive rise with age in the U.S. population has been considered to be a normal accompaniment of aging and not deserving of concern nor reduction. In view of the frequency and uncertainties about predominatly systolic hypertension in the elderly, this will be covered separately.

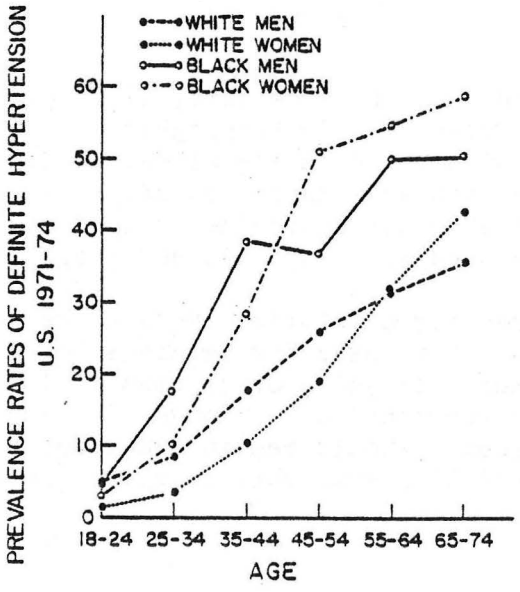
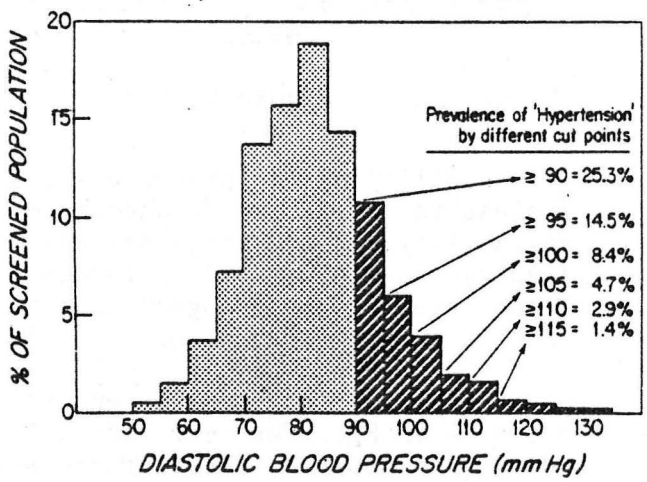


Figure 14



Frequency distribution of diastolic blood pressure at home screen (158, 906 persons; 30–69 years of age). (From "The Hypertension Detection and Follow-up Program." Circulation 40 (5): May 1977 by permission of the American Heart Association, Inc.)

Figure 15

The variability of blood pressure has become more obvious with increasing use of continuous monitoring equipment. Pressures may vary up to 40 mm Hg throughout the day as shown in Figure 16, the data from 20 untreated hypertensives whose pressures were taken continously by intra-arterial line (Miller-Craig, 1978). There is a particularly abrupt rise in pressure upon awakening, a time when patients may be particularly susceptible to cardiovascular catastrophes (Floras *et al*, 1978).

Despite the variability, "casual" blood pressures correlate surprisingly well over time and are valid prognosticators of risk. In Framingham, the highest casual blood pressures show a lesser probability of risk than do the lowest readings but the overall relationship holds true for both (Figure 17). As Kannel emphasizes, "It would seem most unwise to disregard casual blood pressure elevations, even in persons whose basal pressures are found to be substantially lower. They deserve to be followed since they may be expected to progress, and they indicate that attention to risk factors other than blood pressure is warranted" (Kannel, 1977). Others find a similar association between casual and basal pressures with CV risks (Caldwell *et al*, 1978).

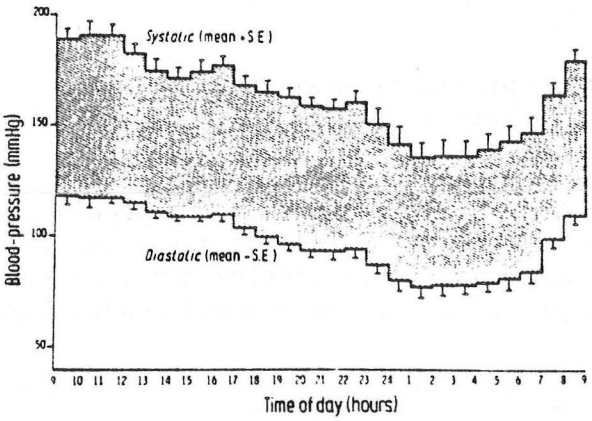


Figure 16

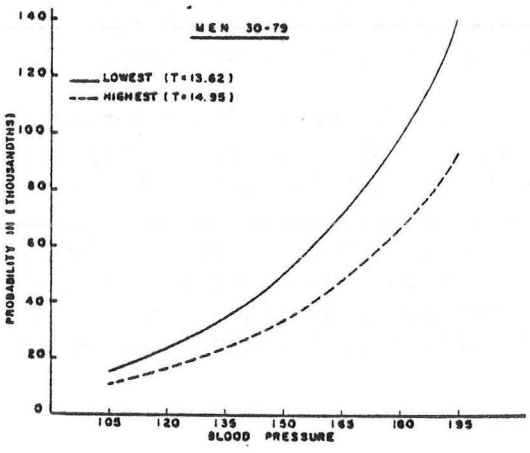


Figure 17

Lability of the pressure should be expected and, in large part, disregarded (unless the suspicion of pheochromocytoma is warranted). In Framingham, variability was inconsistent, was more obvious with those having higher readings than those with borderline levels and increased with age (Kannel *et al*, 1979). These investigators suggest that the term "labile" hypertension be dropped and that an average of 3 readings during an exam be used for diagnosis and prognosis.

The term "labile hypertension" has been used for diastolic levels above and below 90 mm Hg. The term "borderline hypertension" is used for readings between 140/90 and 160/100, but that too seems a misnomer. If the average diastolic is above 90 mm Hg, it seems best to call that "hypertension." Though all patients above that level need not be treated, they obviously should remain under observation and probably should be advised to reduce calories if overweight, restrict dietary sodium, and increase physical activity.

Systolic or diastolic: which is the better determinant of risk: Though the diastolic pressure has traditionally been used for diagnostic and therapeutic decisions, recent data suggest that the systolic is the better determinant of risk for both coronary and cerebral vascular disease (Kannel *et al*, 1971; Rosenman *et al*, 1976; Rabkin *et al*, 1978).

The Framingham data are based upon the annual incidence of various cardiovasculàr events mong 5,127 men and women aged 30 to 62 at entry who have been examined every 2 years since 1949. The data from 18 to 20 years of follow-up include enough cardiovascular (CV) events to provide reasonably narrow 95% confidence limits for the rate of events at various levels of blood pressure (Kannel, 1978). The annual incidence of CV events over 18 years, by level of disatolic and systolic blood pressure at the initial exam for all participants aged 45 to 54 is shown in Figure 18 and for specific CV events in women aged 45 to 74 in Figure 19. In order to simplify their presentation, the data have been mathematically smoothed by using logistic curves. From such curves, two important conclusions have been drawn:

1. As a determinant of risk, the systolic pressure is equal to or better than the diastolic pressure.

2. There is no "normal" level, below which risks do not change; i.e., the lower the pressure, the lower the risk.

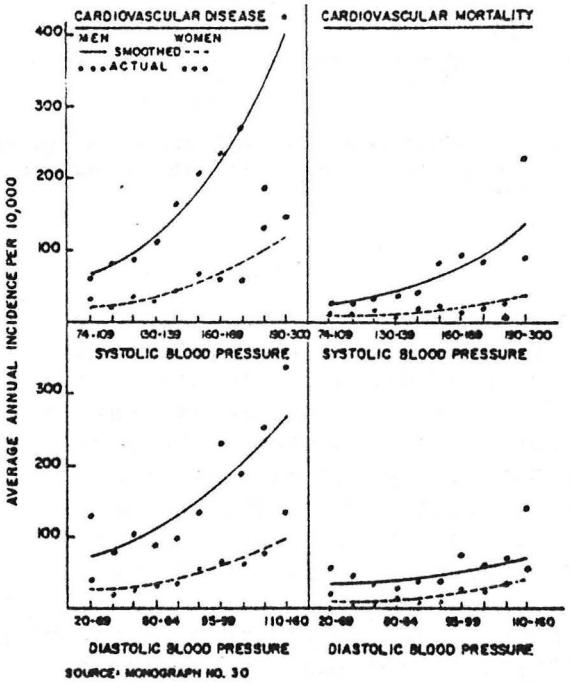


Figure 18

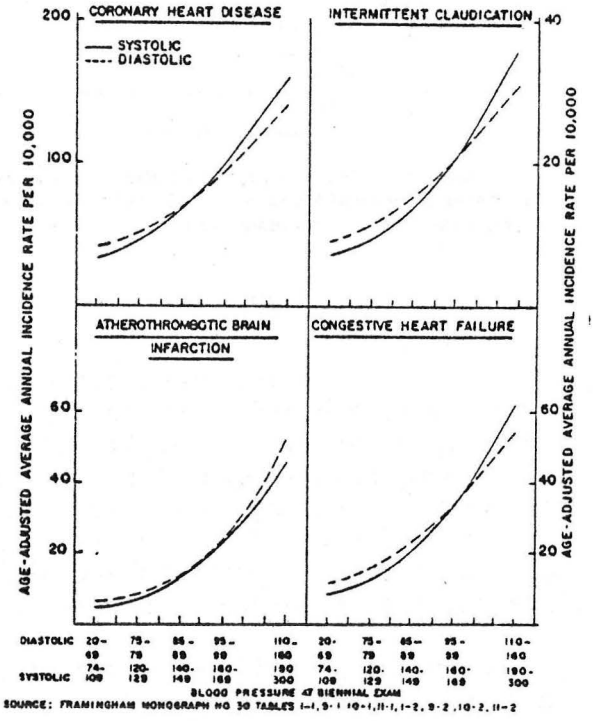
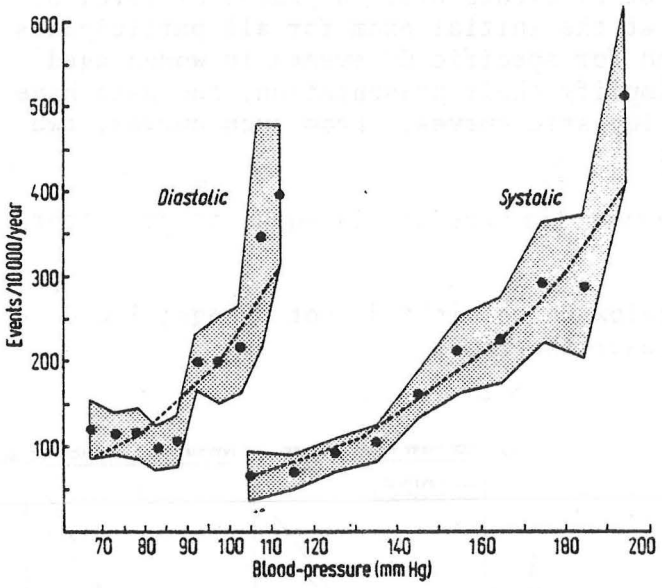


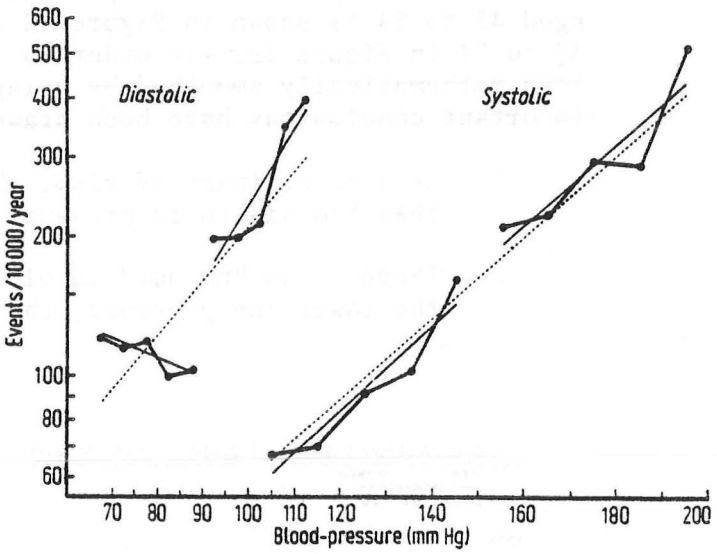
Figure 19

A closer look at the Framingham data suggests different interpretations (Figure 20) (Anderson, 1978). The dotted lines are the smoothed logistic curves, the dots the individual data points (all CV events, 18 years, all ages) and the shaded areas the 95% confidence limits. Notice the 5 dots at the lower left of the diastolic curve. When these data are plotted on a logarithmic vertical scale so that the logistic curves are converted into straight lines (Figure 21), it is obvious that the regression line for the diastolic pressures from below 70 to 89 does not fit the logistic curve; if anything, the reverse slope shows that the incidence of CV events seems to fall with increasing diastolics between 70 and 89 mm Hg.



Annual incidence of cardiovascular events at Framingham over 18 years of follow-up, by level of blood-pressure, all ages, mean of male and female rates.

Figure 20



Same data as in fig. 1, plotted on logarithmic vertical scale so that the logistic curves (broken lines) are now straight lines.

Figure 21

Thus, the relationship between diastolic pressure and CV morbidity is more complicated and there may very well be a threshold of normality. Note how sharply the risk rises at diastolics above 90 mm Hg, suggesting that this is the appropriate lower limit of normal. For systolic pressure the risks do rise with increasing levels over the entire range, suggesting that it may be the better figure to use in assessing risk. In fact, the diastolics *above 90* have the steeper regression and highest correlation coefficients and are therefore the most accurate in predicting the probability of a future CV event.

A recently published papar suggests an *increase* in myocardial infarctions in severely hypertensive patients when diastolic levels were reduced below 90 mm Hg, *taken as the fourth Korotkoff sound* and therefore equal to about 80 mm Hg as we record the blood pressure (Stewart, 1979). Though there may be danger from too great a lowering of the blood pressure, I strongly believe the widely advocated goal of 90 mm Hg for the diastolic remains appropriate. Risk is clearly increased above that level.

REFERENCES: The prevalence of hypertension

Anderson TW. Re-examination of some of the Framingham blood-pressure data. Lancet 1978; 2:1139-1141.

Caldwell JR, Schork MA, Aiken RD. Is near basal blood pressure a more accurate predictor of cardiorenal manifestations of hypertension than casual blood pressure? J Chron Dis 1978; 31:507-512.

Floras JS, Jones JV, Johnston JA, Brooks DE, Hassan MO, Sleight P. Arousal and the circadian rhythm of blood pressure. Clin Sci Mol Med 1978; 55: 395s-397s.

Goldman R. Prevalence and ethnicity of hypertension in New Mexico. Prev Med 1979; 8:165.

Kaplan NM. Essential hypertension. In: Clinical Hypertension. 2nd edition, Baltimore: Williams & Wilkins, 1978.

Kannel WB. Importance of hypertension as a major risk factor in cardiovascular disease. In: Genest J, Koiw E, Kuchel O, eds. Hypertension. New York: McGraw-Hill, 1977:888.

Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease: the Framingham study. Am J Cardiol 1971; 27:335-346.

Kannel WB, Sorlie P, Gordon T. Labile hypertension: a faulty concept? The Framingham study. Am J Cardiol 1979; 43:419.

Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978; 1:795-797.

Pickering G. Hypertension. Definitions, Natural Histories and Consequences. Am J Med 1972; 52:570-584.

Rabkin SW, Mathewson AL, Tate B. Predicting risk of ischemic heart disease and cerebrovascular disease from systolic and diastolic blood pressures. Ann Intern Med 1978; 88:342-345.

Rosenman, Sholtz RI, Brand RJ. A study of comparative blood pressure measures in predicting risk of coronary heart disease. Circulation 1976; 54:51-58.

Schreiber L, Williams S, Rollason D. Survey of hypertension in Spanish-American population of northern New Mexico. Prev Med 1979; 8:226.

Stewart IMG. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. Lancet 1979; 1:801-865.

THE RISKS OF HYPERTENSION:

It doesn't take much hypertension to increase the risk for CV disease. The actuarial data of over 4 million people insured by 26 American companies, published in 1959, show the increase in mortality which occurred in people with relatively little elevation of either systolic or diastolic levels (Table 11) (Society of Actuaries, 1959). As in all such data, women tolerate hyperension better than men, requiring at least a 10 mm Hg higher level to achieve the same degree of morbidity or mortality.

TABLE 11

Variations in Mortality Among Men and Women, Aged 15 to 69, According to Systolic and Diastolic Blood Pressures

Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Mortality Ratio (%)*	
		Men	*Women*
128 to 137	<83	109	101
	83 to 87	127	107
	88 to 92	140	123
	93 to 97	168	110
	98 to 102	197	—
138 to 147	<83	141	118
	83 to 87	153	122
	88 to 92	170	120
	93 to 97	199	195
	98 to 102	244	220
148 to 157	<88	180	120
	88 to 92	191	160
	93 to 97	224	163
	98 to 102	269	232
158 to 167	<88	215	214
	88 to 92	240	208
	93 to 97	268	287
	98 to 102	289	(362)

The Framingham data demonstrate the progressive rise in morbidity and mortality with increasing systolic and diastolic pressures in both men and women (Figure 22). The incidence of all cardiovascular disease increases with the blood pressure (Figure 23) as does the incidence of the major manifestations of coronary disease (Figure 24) (Kannel, 1977). An even sharper increment in the incidence of stroke is noted in the presence of hypertension (Figure 25) (Kannel *et al*, 1976).

About 2/3 of the victims of the major cardiovascular diseases have hypertension, defined as a blood pressure of 140/90 or higher. Although the relative impact of hypertension is greater for stroke and congestive failure, the absolute risk is greatest for coronary heart disease. Hypertensives aged 45 to 74 have twice more peripheral vascular disease, almost 3 times more coronary disease, 5 times more congestive failure, and about 8 times more strokes as do normotensives (Kannel, 1977).

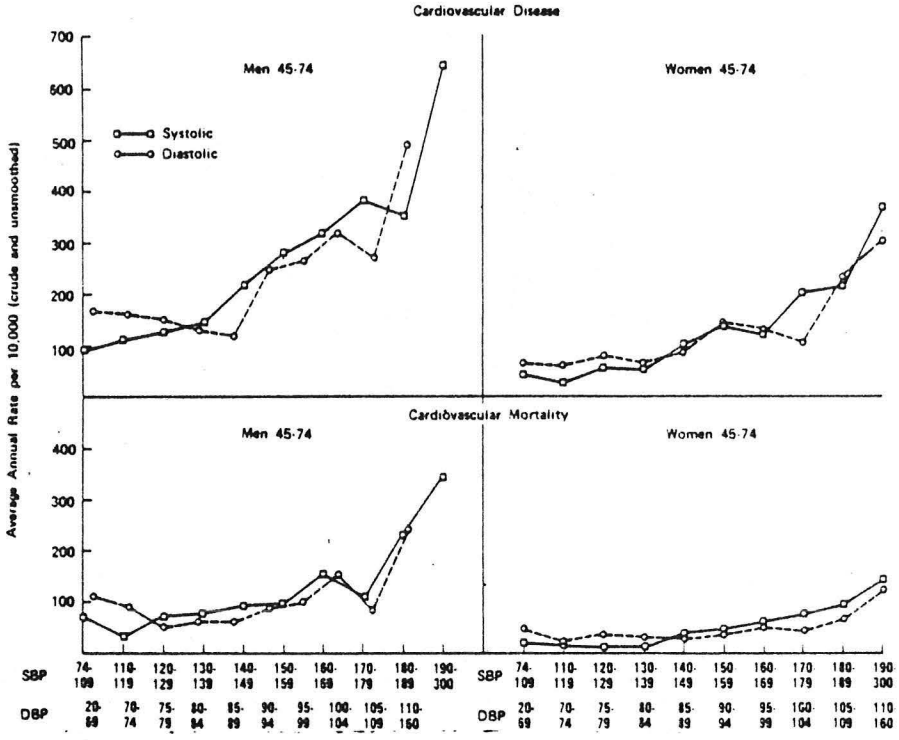
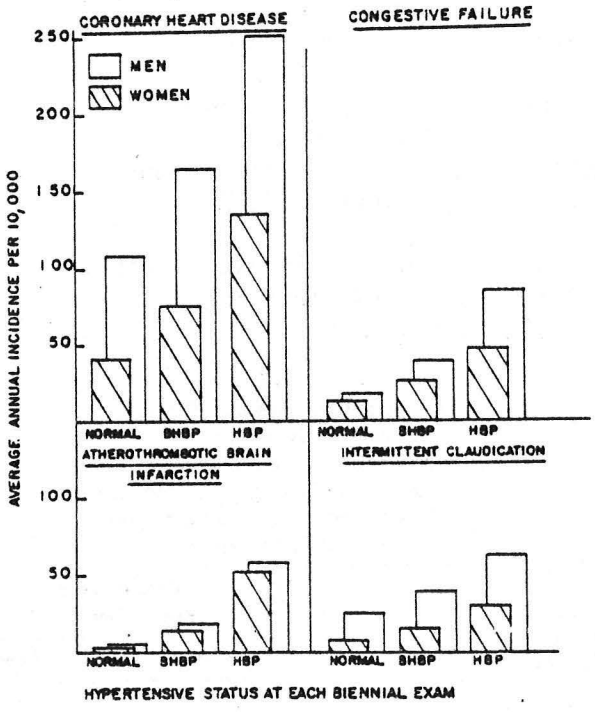
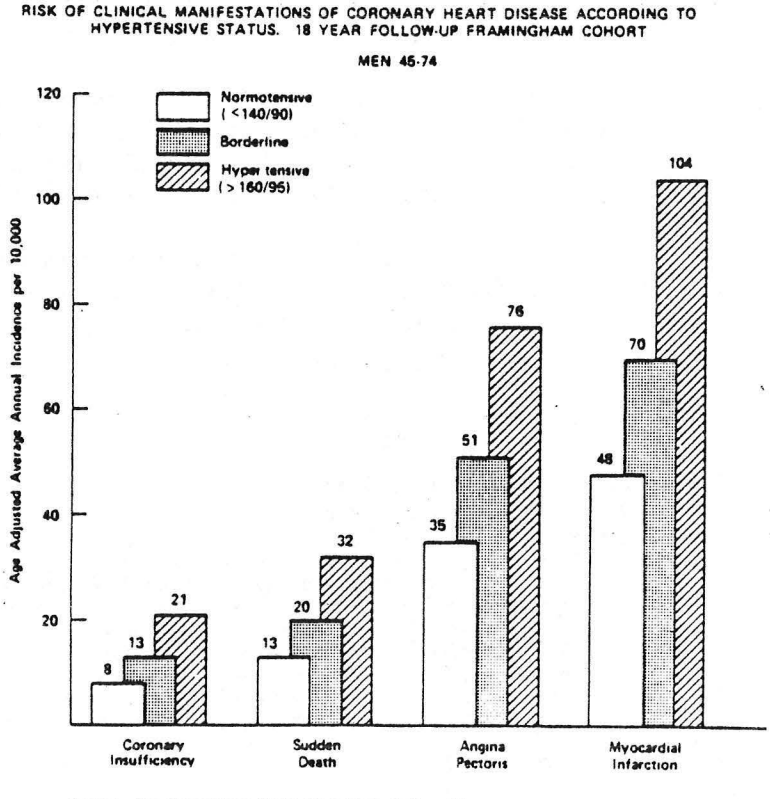


Figure 22



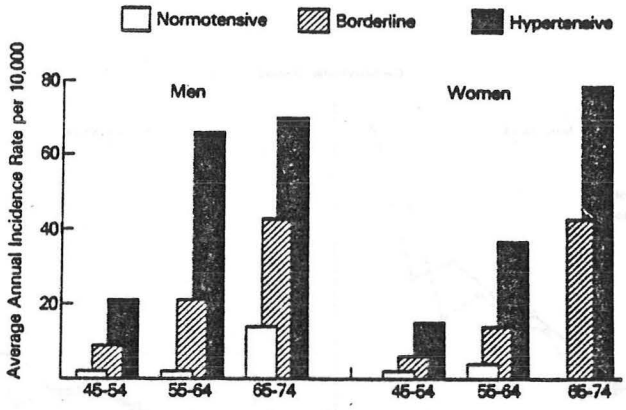
Risk of cardiovascular morbidity according to hypertensive status at each biennial exam, in men and women aged 45 to 74, Framingham Study, 20-year follow-up.

Figure 23



Source: The Framingham Study Monograph, Section 30

Figure 24



Average annual incidence rate for atherothrombotic brain infarction by hypertensive status: Framingham study, 18-year follow-up.

Figure 25

Let us examine in more detail the associations of hypertension with heart disease and stroke.

Heart disease: Before the end results of long-standing hypertension become manifest as an MI or congestive failure, the heart goes through anatomical and functional changes. Electrocardiographic evidences of left atrial and ventricular hypertrophy (LVH) have been the earliest findings but they actually reflect long-standing and serious involvement. In Framingham the presence of LVH on ECG was an ominous sign: within 5 years, 32% of men with ECG-LVH died of a cardiovascular catastrophe and congestive heart failure developed 10 times more frequently among all patients with LVH (Table 12).

These ECG (and X-ray) findings of cardiac invlvement are relatively insensitive: 52% of men and 41% of women who had a cardiovascular event (angina, MI, sudden death, or CHF) had a normal ECG and chest X-ray on their last exam which was less than 2 years before (Table 13) (Kannel, 1977).

The more sensitive echocardiogram will detect cardiac involvement earlier and more frequently: in 234 patients with mild to moderate hypertension (mean BP = 150/95), 61% had an abnormality (Savage *et al*, 1979)(Table 14).

TABLE 13 →

TABLE 12

Five-year Mortality Rates According to ECG-LVH, Men and Women Aged 45 to 74, Framingham Study, 18-year Follow-up

	5-year Age-adjusted Mortality Rates (per 100)							
	Cardiovascular Mortality Rate		*Coronary Mortality Rate*		*Sudden Death*		*Overall Mortality Rate*	
ECG-LVH	Men	Women	Men	Women	Men	Women	Men	Women
None	3.58	1.62	1.44	0.52	0.80	0.19	6.70	3.62
Possible*	11.06	5.24	3.73	0.97	2.11	0.36	16.39	8.58
Definite†	31.85	16.43	9.50	1.80	5.53	0.68	37.57	19.71

* Possible = voltage criteria
† Definite = voltage criteria plus ST + T abnormality

Percent of Cardiovascular Disease Developing in Hypertensive Individuals Prior to Evidence of Target Organ Involvement,* Men and Women Aged 35 to 64, Framingham Study, 16-year Follow-up

	Percent Free of Prior Abnormality	
Ages	*Men*	*Women*
35 to 44	78	50
45 to 54	45	42
55 to 64	45	39
Total	52	41

* Target organ involvement—ECG abnormal (LVH; IV block; NSA S-T and T) cardiac enlargement on x-ray

Prevalence of Echocardiographic Abnormalities in 234 Hypertensive Subjects

TABLE 14

Echocardiographic measurement	Percent of patients*
Ventricular septal thickness	50
Left ventricular free-wall thickness	61
Disproportionate septal thickening	4
Left ventricular mass	51
Left ventricular transverse dimension at end-diastole	5
Left ventricular transverse dimension at end-systole	12
Left atrial dimension	5
Aortic root dimension	7
Ejection fraction	15
Percent fractional shortening	13
Mitral valve E-F slope	6

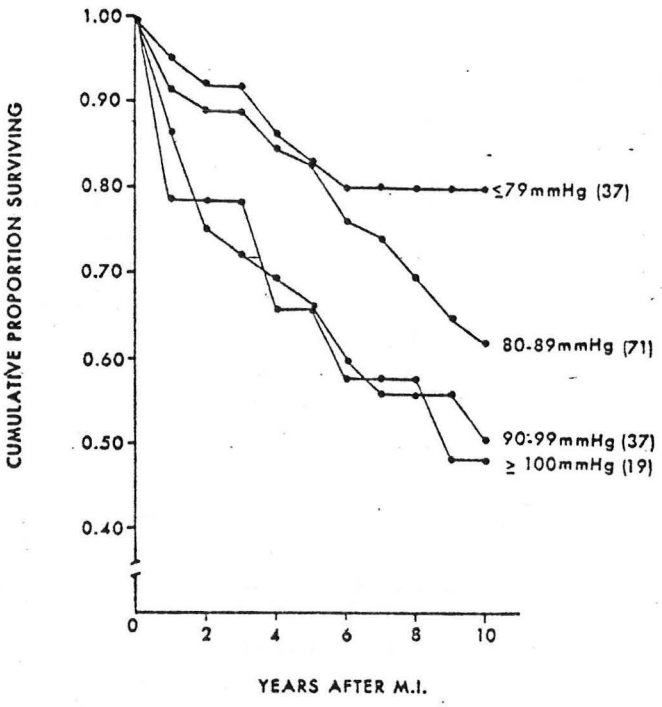


Figure 26

In patients having an acute myocardial infarction, survival is closely related to the diastolic blood pressure before infarction (Figure 26)(Rabkin *et al*, 1977). If the patient's blood pressure was not known before the MI, it may be deceptively lower after MI, obscuring the recognition of risk and the need for more careful follow-up for return of the hypertension. Over a 5-year follow-up of 288 men having an MI, the mean BP level fell 7.7/3.4 and often remained lower for months afterward, without obvious relation to weight loss, heart failure, etc.(Coronary Drug Group, 1979).

Congestive heart failure is closely related to hypertension and is a serious complication: in Framingham, hypertension preceded CHF in 75% of cases; once CHF developed, 60% of men and 40% of women died within 5 years (Kannel, 1977).

Stroke: The risk for stroke is greatly increased by the presence of hypertension, particularly strokes caused by cerebral hemorrhage (Abu-Zeid *et al*, 1977). Many patients having a stroke have previously unrecognized or untreated hypertension: of 65 patients admitted to Whittington Hospital in London over an 8-month interval in 1977 with a completed stroke, 35 were hypertensive and 23 of these were not under good control (Kennedy & Hoffrand, 1978).

As with MI, the prognosis after a stroke is closely related to the prior blood pressure, more so with the systolic level for stroke (Figure 27) (Rabkin *et al*, 1978a) whereas the diastolic level is more predictive of prognosis after an MI (Figure 26). In the Manitoba study of 3,983 men over 26 years of age, the chance for stroke was particularly related to a *rise* in systolic blood pressure during the preceding 5 years (Rabkin *et al*, 1978b).

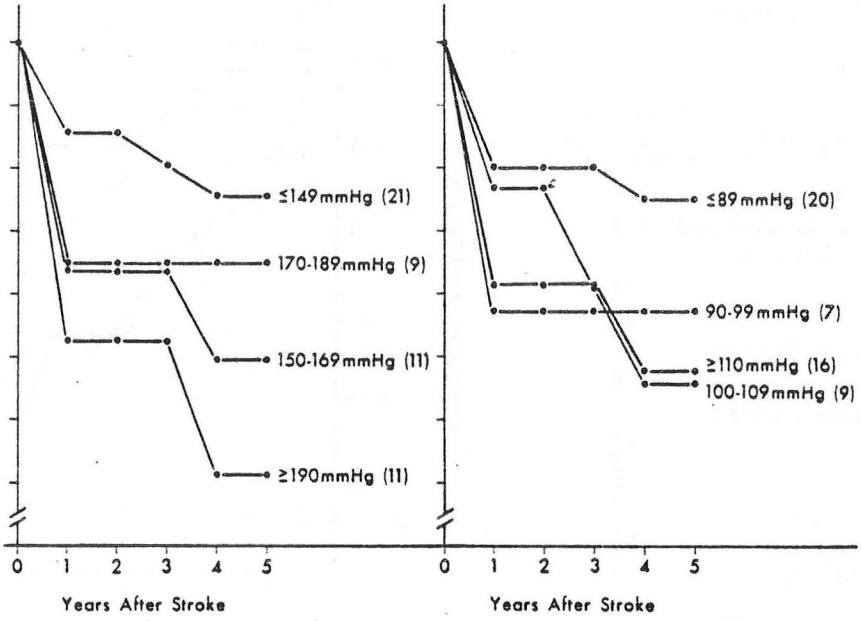


Figure 27

These close relationships to the systolic blood pressure and the overall close associations of hypertension to stroke suggest that the height of the blood pressure *per se* is the critical factor. Though hypertension likely accelerates atherosclerosis in cerebral vessels as elsewhere (Araki *et al*, 1978), the pathological features of the arterial lesions responsible for brain damage (microaneurysms, intramural fibrin and lipid deposition, etc.) and the location of these lesions suggest that they arise from mechanical distension (Ross Russell, 1975). The process is similar to what happens in acute experimental hypertension wherein vascular resistance breaks down, the vessel wall loses its integrity, and plasma insudes into the wall, finally leading to occlusion or rupture. In keeping with this concept involving abnormal autoregulation of cerebral blood flow (CBF), hypertensive patients were unable to increase CBF when given 5% CO_2 to breathe even though their flows were normal at normocapnia (Griffith *et al*, 1978).

REFERENCES: *The risks of hypertension*

Abu-Zeid HAH, Choi NW, Maini KK, Hsu PH, Nelson NA. *Relative role of factors associated with cerebral infarction and cerebral hemorrhage. Stroke 1977; 8:106-112.*

Araki G, Mihara H, Mizukami M, Kin H, Nishijima M, Yoshida Y. *Comparative angiographic and histological evaluations of intracranial atherosclerosis in hypertensive and normotensive subjects. Stroke 1978; 9:364-327.*

Coronary Drug Project Research Group, University of Maryland, Baltimore, Maryland. *Blood pressure decrease following a recurrent myocardial infarction. Abstracts, Conference on CVD Epidemiology, New Orleans, March 19-21, 1979, p. 63.*

Griffith DNW, James IM, Newbury PA, Wollard ML. Abnormal cerebrovascular regulation in hypertensive patients. Br Med J 1978; 3:740.

Kannel WB, Dawber TR, Sorlie P, Wolf PA. Components of blood pressure and risk of atherothrombotic brain infarction: the Framingham study. Stroke 1976; 7:327-331.

Kennedy PGE, Hoffbrand BI. Strokes and hypertension: contribution of poor blood pressure control. Br Med J 1978; 2:1605.

Rabkin SW, Mathewson FAL, Tate RB. Prognosis after acute myocardial infarction: relation to blood pressure values before infarction in a prospective cardiovascular study. Am J Cardiol 1977; 40:604-610.

Rabkin SW, Mathewson FAL, Tate RB. The relation of blood pressure to stroke prognosis. An Intern Med; 1978; 89:15-20. (a)

Rabkin SW, Mathewson FAL, Tate RB. Long term changes in blood pressure and risk of cerebrovascular disease. Stroke 1978; 9:319-327. (b)

Ross Russell RW. How does blood-pressure cause stroke? Lancet 1975; 2:1283-1285.

Savage DD, Drayer JIM, Henery WL, Mathews EC, Jr., Ware JH et al. Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. Circulation 1979; 4:623-632.

Society of Actuaries. Build and blood pressure study, 1959.

HYPERTENSION IN THE ELDERLY

Diastolic hypertension

At whatever age, diastolic blood pressures above 90 mm Hg are associated with an increased risk of cardiovascular events (Table 15). Data from the VA Cooperative Study further portray the danger: among men with diastolic pressures between 90 to 114 mm Hg, the following percentages developed a major cardiovascular complication during an average five years on placebo:

Age < 50 - 15.2%

Age 50-59 - 26.9%

Age > 60 - 62.8%

Fortunately, antihypertensive therapy is effective in the elderly with diastolic hypertension and, if used with reasonable care, is no more likely to cause bothersome side effects. In the VA Study, therapy was 54% effective in reducing cardiovascular morbidity in those over 60 years of age, a reduction identical to that observed in those under age 50 (VA Cooperative Study, 1972). The elderly with diastolic hypertension will usually tolerate a slow, gradual reduction in pressure with little or no more postural hypotension or other side effects than younger patients. With diuretic therapy of 319 men, most in their 70's and 80's, the frequency of postural hypotension was 4.6% compared to an incidence of 3.4% in non-treated men of similar age (Myers *et al*, 1978). On the other hand, if potent adrenergic inhibitors or vasodilators are given to elderly people in large doses, they will develop dizziness and other manifestations of cerebral ischemia (Jackson *et al*, 1976). The likelihood is probably greater for these symptoms to appear in the elderly since, with more sclerotic vessels, they are unable to autoregulate cerebral blood flow (CBF) as quickly as younger people, so that a fall in pressure may significantly lower CBF (Jones & Graham, 1978).

Pseudohypertension

Sometimes significant postural dizziness occurs after antihypertensive drug therapy because the patient was not hypertensive to begin with, but rather had "pseudohypertension" due to rigid vessels which could not be adequately occluded with the sphygmomanometer cuff. When direct intra-arterial readings are taken, the levels may be much lower (Spence *et al*, 1978). One example from Spence's paper is a reading of 245/120 with the cuff, but 184/86 with the direct recording. The possibility of pseudohypertension should be suspected in elderly people whose vessels feel rigid, who have no vascular damage in the retina or elsewhere despite seemingly high blood pressure readings, and who suffer inordinate postural symptoms despite cautious therapy. If one is suspicious, a direct intra-arterial reading should settle the issue.

TABLE 15

Risk of Cardiovascular Events According to Diastolic Blood Pressure in Men and Women 45–74. Framingham Heart Study: 18 Year Follow-Up

	AVERAGE ANNUAL INCIDENCE PER 1,000 POPULATION					
	Men			Women		
AGE	<90	90–109	≥110	<90	90–109	≥110
45–54	9.5	17.7	33.6	3.0	5.9	13.6
55–64	18.0	37.7	62.2	10.2	15.6	39.4
65–74	24.2	42.9	55.6	17.2	32.4	54.5

Predominantly systolic hypertension

Thus, both the risks of untreated diastolic hypertension and the benefits of its therapy are similar in the elderly as the younger patient. But the more common finding is an elevated systolic reading with a normal diastolic level, i.e. pure or predominant systolic hypertension (Table 16). This reflects the tendency for a progressive rise in the systolic pressure as people grow older, whereas the diastolic level seldom advances beyond age 40 (Figure 28) (Kaplan, 1978). The systolic rise is largely the result of a loss of elasticity in the aorta and major resistance vessels. The reduced aortic distensibility leads to a steeper slope of pressure rise per milliliter of blood ejected with each heart beat (Tarazi, 1978).

TABLE 16

Prevalence of Pure Systolic Hypertension by Age, Sex, and Race. National Health Examination Survey, United States 1960–1962

	% PURE SYSTOLIC HYPERTENSION			
	Men		Women	
AGE	White	Black	White	Black
25–34	0.3	1.0	0.2	0.0
35–44	0.9	0.6	0.9	1.5
45–54	3.5	1.3	4.6	7.6
55–64	9.5	13.0	15.6	4.3
65–74	15.0	25.5	30.7	38.9
75–79	26.9	38.6	32.9	43.1

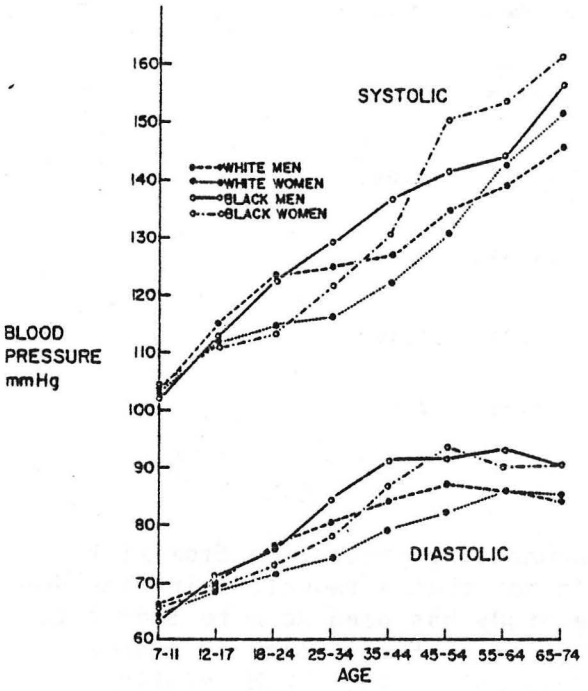


Figure 28

The hemodynamic pattern of systolic hypertension in the elderly is an increase peripheral resistance with low plasma volume and low-normal cardiac output (Adamopoulos *et al*, 1975). In addition, the baroreceptor mechanism become less sensitive with age, reducing the ability to buffer swings in pressure. These factors influence the response to therapy.

The risk of systolic hypertension

Before discussing therapy, it should be emphasized that pure systolic hypertension poses a serious risk, regardless of age. Studies done in Chicago document the risk (Dyer *et al*, 1977). In white men age 40-59 who were followed for 15 years (Table 17) those with pure systolic hypertension (Group 3) had overall and cardiovascular mortality rates much higher than those without systolic elevations (Group 1) and almost as high as those with diastolic hypertension (Group 2). The

overall difference in death rate was about 2 fold. In the study described in Table 18, the 3-year risks of coronary and all cardiovascular deaths and strokes were determined for people aged 65 to 74. Here again, those with pure systolic hypertension (Group 3) had about 2 fold more mortality and stroke morbidity.

TABLE 17

Baseline Blood Pressure Status and 15 Year Mortality of 1233 White Males Age 40–59 and Free of Definite Coronary Heart Disease in 1958. Chicago Peoples Gas Company Study

BLOOD PRESSURE STATUS	N	DEATH ALL CAUSES		CVR DEATH**		CORONARY HEART DISEASE DEATH	
		Events	Rate*	Events	Rate	Events	Rate
1 - Systolic<140 Diastolic< 90	782	119	163	61	83	44	58
2 - Diastolic≥ 90	257	90	323	49	174	33	117
3 - Systolic≥140 Diastolic<90	194	58	277	30	156	21	118
Rate Ratio: 3 vs 1			1.70		1.88		2.03

*Per 1,000 population, age-adjusted by 5-year age groups to the whole cohort
**Cardiovascular-renal causes

TABLE 18

BLOOD PRESSURE AND 3-YEAR RISKS IN PATIENTS, 65 TO 74

(Chicago Stroke Study: Shekelle et al. Stroke 5:71, 1974)

Blood Pressure	No.	Coronary Deaths	C-V-R Deaths	Stroke
1. Syst <180 Diast <95	1,973	8.0%	11.1%	5.0%
2. Diast >95	493	9.0%	14.9%	8.8%
3. Syst >180 Diast <95	224	13.5%	22.0%	13.4%
Ratio 3 vs 1		1.69	1.96	2.53

The therapy of systolic hypertension

The risk is real but there are no data documenting protection from risk by reduction of the high systolic levels. It's not that a reduction in risk does not follow therapy but rather that no adequate study has been done to find out. One small, poorly controlled study showed a reduction of mortality by almost half with just thiazide diuretic therapy (Priddle *et al*, 1968). Hopefully, studies now being conducted in Europe and the U.S. will soon provide the data needed to decide if therapy is worthwhile.

For now, I believe an attempt should be made to reduce the systolic pressure in all patients to below 180 mm Hg, since the risk is so great. Therapy should be slow and gradual, "gentle seduction rather than an acute battle" (Editorial, Lancet, 1977). These precautions are advised:

1. Diuretics seem the best initial therapy but, since plasma volume may already be low, the doses should be small. Watch for hypokalemia particularly in those who don't eat well (Editorial, Br Med J, 1978).

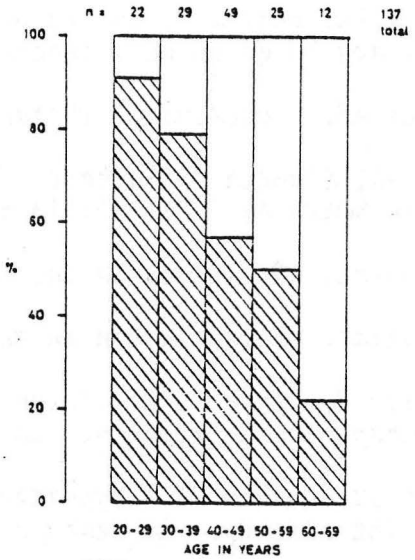
2. Adrenergic inhibitors should be used in small doses so as not to reduce cardiac output too much and therby plummet pressures in the rigid aorta. Avoid guanethidine and others which may cause postural hypotension since the insensitive baroreceptor mechanism may not buffer a falling pressure quickly. Beta-blockers may not work as well in the elderly (Buhler *et al*, 1975) (Figure 29) whether because they have lower renin levels or because they have fewer beta-receptors. Note that, whereas 90% of those in their 20's responded to beta-blockers alone, only about 20% of the 60-year-old hypertensives did as well. With a diuretic, beta-blockers will probably work much better.

3. Vasodilators, without adrenergic blockadė, may precipitate angina (Traub *et al*, 1979).

4. With therapy, the systolic pressure will likely fall more than the diastolic but it may not be possible to achieve a systolic pressure below 160 without postural symptoms (Seligman *et al*, 1977). The goal of 160 seems appropriate and perhaps even 170 is adequate to remove most of the extra risk.

Stroke survivors

Some are hesitant to treat those hypertensives who have survived a stroke, fearing that any lowering of pressure may worsen cerebral blood flow and incur a second stroke. Recall that the risk of stroke is strongly related to the level of the blood pressure. And two well-controlled studies have clearly shown that effective antihypertensive therapy will sharply reduce stroke recurrences (Beevers *et al*, 1973; Carter, 1975). In Beever's study, the recurrence of stroke and the development of congestive failure were markedly diminished in those who achieved good control (Figure 30).



The percent of 137 hypertensive patients in various age groups whose diastolic blood pressure was reduced to 95 mm Hg or less by monotherapy with β-blockers. (From Bühler, F. R., et al.: Antihypertensive beta-blocking action as related to renin and age. A pharmacological tool to identify pathogenetic mechanisms in essential hypertension, Am. J. Cardiol. 36:653, 1975. Used by permission.)

Figure 29

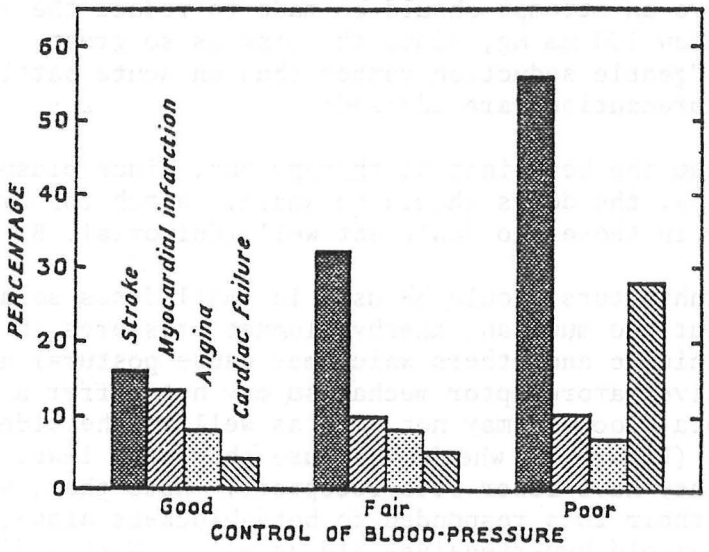


Figure 30

REFERENCES: *Hypertension in the elderly*

Adamopoulos PN, Chrysanthakopoulis SG, Frohlich ED. Systolic hypertension: nonhomogeneous disease. Am J Cardiol 1975; 36:697701.

Beevers DG, Hamilton M, Fairman MJ, Harpur JE. Antihypertensive treatment and the course of established cerebral vascular disease. Lancet 1973; 1:1407-1409.

Buhler FR, Bertel O, Lutold BE. Simplified and age-stratified antihypertensive therapy based on beta blockers. Cardiovascular Med 1978; 3:135-148.

Carter AB. Hypotensive therapy in stroke survivors. Lancet 1970; 1:485-490.

Dyer AR, Stamler J, Shekelle RB et al. Hypertension in the elderly. Med Clin Nwrth Am 1977; 61:513-529.

Editorial. Diuretics in the elderly. Br Med J 1978; 1:1092-1093.

Editorial. Hypertension in the elderly. Lancet 1977; 1:684-485.

Jackson G, Mahon W, Pierscianowski TA, Condon J. Inappropriate antihypertensive therapy in the elderly. Lancet 1976; 2:1317-1318.

Jones JV, Graham DI. Hypertension and the cerebral circulation--its relevance to the elderly. Am Heart J 1978; 96:270-271.

Kaplan NM. Approach to the hypertensive patient. In: Clinical Hypertension. 2nd ed, Baltimore, Williams & Wilkins, 1968; pg 10.

Myers MG, Kearns PM, Kennedy DS, Fisher RH. Postural hypotension and diuretic therapy in the elderly. Canadian Med Assoc J 1978; 119:581-585.

Priddle WW, Liu SF, Breithaupt DJ, Grant PG. Amelioration of high blood pressure in the elderly. J Am Geriatrics Soc 1968; 16:887-892.

Seligman AW, Alderman MH, Engelland AL, Davis TK. Treatment of systolic hypertension. Clin Res 1977; 25:254A. (abstract)

Spence JD, Sibbald WJ, Cape RD. Pseudohypertension in the elderly. Clin Sci Mol Med 1978; 55:399s-402s.

Tarazi RC. Should you treat systolic hypertension in elderly patients? Geriatrics 1978; 33:25-29.

Traub YM, Aygen MM, Rosenfeld JB. Hazards in treatment of systolic hypertension. Am Heart J 1979; 97:174-177.

VA Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure and prior cardiovascular disease. Further analysis of side effects. Circulation 1972; 45:991.

MANAGEMENT OF THE "MILD" HYPERTENSIVE

Is Therapy Needed?

Most hypertensives have "mild" disease defined as diastolic blood pressures from 90 to 105 mm Hg and little if any target organ damage. Their short-term prognosis is excellent but, if left untreated, after many years they will develop various cardiovascular sequelae and die prematurely.

Even though it may take them a long time to get into trouble, the "mild" hypertensives comprise the major population in whom prevention can be effective. Based upon the frequency distribution of diastolic hypertension (Figure 15) and the mortality rates in the Framingham population (Figure 22), the largest number of unnecessary deaths are attributable to "mild" hypertension (Figure 31) (Smith, 1979).

If those with diastolic pressures between 90 and 109 mm Hg were controlled and their risks thereby alleviated, considerable reduction of morbidity and mortality would follow. Labarthe has analyzed the impact of reversal of risk for stroke, coronary heart disease and overall mortality by control of hypertension (Table 19) (Labarthe, 1979). If all those with diastolics above 90 mm Hg were controlled, the "community impact" would be considerable, as measured by the total number of such events in the total population which could be prevented: 37% of strokes, 21% of coronary events and 26% of total mortality. If only those with diastolics above 110 were controlled, much less of an overall impact would be seen. The column "Clinical Impact" in Table 19 shows that for people with these levels of hypertension, a greater reduction in morbidity would follow control of the higher levels since so many more events would occur among those with the higher levels.

One more factor should be considered in deciding upon the need for therapy: the rate of increase in blood pressure over a 15 to 17 year follow-up was greater the higher the initial pressure (Miall and Chinn, 1973). Thus by

Death due to Hypertension

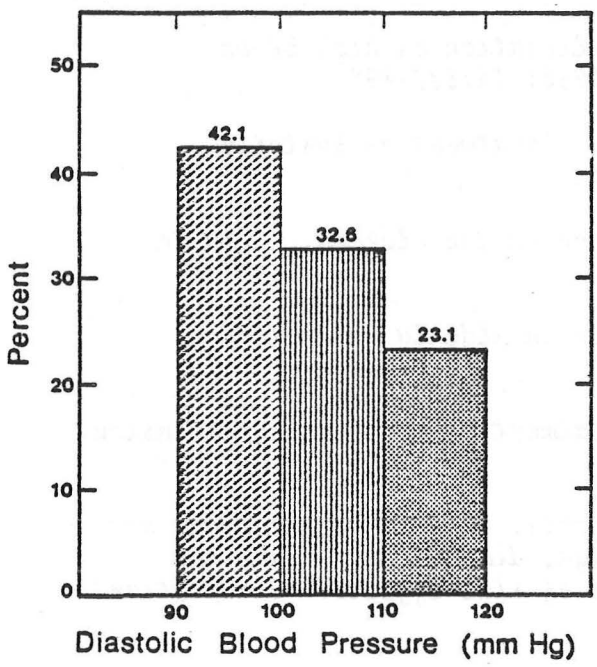


Figure 31

TABLE 19

Estimates of Possible Impacts on Rates of Events If Risk Associated with Hypertension Were Reversed

Event	Diastolic Blood Pressure (mm Hg)	Clinical Impact* (%)	Community Impact† (%)
CVA	110+	82.9	18.1
	90+	56.7	37.1
CHD	110+	47.5	4.2
	90+	37.5	21.1
Death	110+	63.3	8.0
	90+	43.6	25.8

Adapted from Labarthe et al.,[13] with permission.
* (Reduction in events/Events expected in blood pressure stratum) × 100.
† (Reduction in events/Events expected in total population) × 100.

preventing a progressive rise in pressure, control of early hypertension--which is usually easy--may protect the patient from the subsequent development of more severe hypertension which may be far more difficult to treat.

Is therapy worthwhile?

Almost everyone agrees that patients with diastolic levels above 105 mm Hg should be treated. The VA Cooperative Study showed a 50% or greater reduction by drug treatment of the rates of serious cardiovascular disease in 190 men with diastolics above 105 (Table 19) (VA Cooperative Study, 1972). However, those 22 men with diastolics between 90 and 104 (listed under "none" in Table 20) had no relief from their already low rate of morbidity in the relatively short time of the study.

A second study, involving 389 men and women with an average blood pressure of only 148/99, excluded those with any prior recognizable cardiovascular involvement--a group that truly can be called "mild " (U.S. Public Health

TABLE 21 →

TABLE 20

Attack Rates and Effectiveness of Treatment in Relation to the Presence of Risk Factors at Entry, Among All Subjects with Diastolic Blood Pressure of 90 to 114 mm Hg

Risk Factors at Entry*	Control Group		Treated Group		Effectiveness of Treatment (%)
	Number Randomized	*Attack Rate*	*Number Randomized*	*Attack Rate*	
None	24	0.066	22	0.069	—
Any one	68	0.171	66	0.087	49
Any two	62	0.363	64	0.138	62
All three	40	0.509	34	0.173	66

Adapted from Circulation 45:991-1004, 1972, with permission.
* Risk factors are (1) age over 50 years, (2) CVR abnormalities, and (3) diastolic blood pressure of 105 to 114 mm Hg.

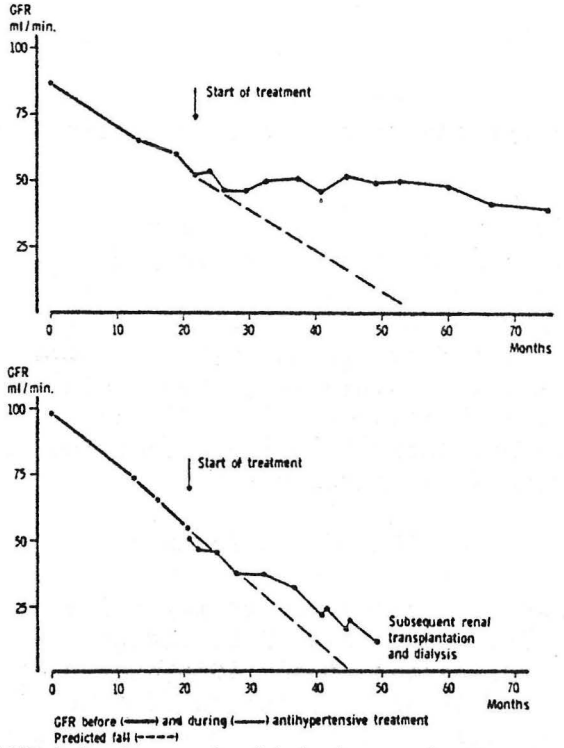
All Morbid Events

	Active		Placebo	
	No.	Rate per 100 patients	No.	Rate per 100 patients
Total patients	193		196	
Total events	72	37.3	127	64.8
Hypertensive	37	19.2	89	45.4
CVA	1	0.5	3	1.5
ECG hypervoltage	9	4.7	24	12.2
LVH by ECG	14	7.3	32	16.3
Cardiomegaly	12	6.2	20	10.2
Retinopathy	1	0.5	8	4.1
Renal insufficiency	0	0.0	1	0.5
Congestive heart failure	0	0.0	1	0.5
Atherosclerotic	35	18.1	38	19.4
Myocardial infarction	9	4.7	8	4.1
Death	2	1.0	2	1.0
Other CHD	22	11.4	28	14.3
Transient ischemic attacks	0	0.0	0	
Peripheral arterial insufficiency	2	1.0	0	
Treatment failures	0		24	12.2
Asymptomatic	0		11	5.6
Symptomatic	0		13	6.6

Service Study, 1977). After 7 to 10 years, the treated group had significantly fewer "hypertensive" complications but the same number of "atherosclerotic" events as did the placebo treated group (Table 21). These "hypertensive" events which were reduced included LVH which we have noted to be a serious risk factor among Framingham hypertensives. Of particular interest in both the VA and USPHS studies is the development of progressive hypertension (i.e. a rise in the diastolic to above 124 or 130 mm Hg, respectively) in 12% of those given placebo but in none of those given drug therapy. Thus, therapy of "mild" hypertension seems to offer benefit.

Two special indications

Hypertensives who are diabetic or who are having transient ischemic attacks may be particularly helped by reduction in their pressure. In a small but carefully followed group of hypertensive diabetics, Mogensen has shown a rapidly progressive fall in renal function, measured by GFR, before therapy and a sharp break in the fall-off after institution of effective therapy (Mogensen, 1976). The course of the GFR in two patients is shown in Figure 32, the top one successfully treated, the lower one unsuccessfully treated (Mogensen 1979).



G.F.R. before (————) and during (————) antihypertensive treatment.

Predicted fall (— — — —) based upon linear extrapolation.

Figure 32

The occurrence of stroke in 199 patients with transient ischemic attacks was clearly related to their diastolic blood pressure, with a lower rate in those receiving antihypertensive drugs (Whisnant *et al*, 1978). Evidence for therapy of hypertensives who've already suffered a stroke has been previously provided.

The question of coronary disease

But the data supporting therapy for "mild" hypertension remains meager. And in neither the VA nor the USPHS studies were coronary events reduced by therapy. There are many possible reasons for this lack of protection:

--The studies were started in middle-aged people who likely had already developed coronary atherosclerosis. In the VA Study, many of the patients already had coronary involvement when started in the trial. A relatively short course of antihypertensive therapy should not be expected to reverse coronary atherosclerosis.

--In order to isolate and examine the effects of antihypertensive therapy, none of the other risk factors (smoking, cholesterol, etc.) were altered.

--The number of patients was too small and the duration of the studies too short to demonstrate effects which may take many years to become obvious.

The choice of therapy

Another possible factor was the choice of therapy which was a thiazide diuretic, reserpine, and, in the VA Study, hydralazine if needed. Protection from myocardial infarction was provided to a group of 635 Swedish men with diastolics above 115 mm Hg by therapy which included a beta-blocker in 78% (Berglund *et al*, 1978) (Figure 33). The study was not carefully controlled with no matching of the 635 treated and 391 untreated patients. On the other hand, a smaller study from Australia found an increase in MI's among the 62 of 206 elderly men with milder hypertension (diastolic blood pressure 95 to 110) given thiazide therapy compared to the remainder given beta-blockers (Morgan et al, 1972). The issue is not settled: in a study using various drugs among 1247 Scots, the frequency of strokes and myocardial infarction was lowered best by combined diuretic plus beta-blocker therapy (Beevers *et al*, 1978). The frequency of MI's and angina with varying regimens was:

	Diuretic	Beta-Blocker	Diuretic + Beta-blocker	Other Drugs
Men (579)	8.8%	5.2%	2.9%	11.7%
Women (688)	9.0%	9.5%	4.8%	8.6%

The authors conclude that no one group of drugs conferred any extra benefits in preventing coronary disease but rather that the degree of control was the major determinant.

Beta-blockers may protect both hypertensives (Stewart, 1976) and non-hypertensives (Wilhelmsen, 1974) from myocardial infarction, presumably by their anti-arrhythmic action and their decrease in myocardial work, as well as by their reduction in blood pressure. Another reason for the potential advantage of beta-blocker therapy is the protection from hypokalemia they offer: by themselves, beta-blockers may raise plasma K^+; with diuretics, they diminish the degree of hypokalemia (Neuvonen, 1978). Since Holland *et al* (1979) have clearly shown that thiazide-induced hypokalemia may activate serious ventricular arrhythmas, the protection offered by beta-blockers may involve this, too.

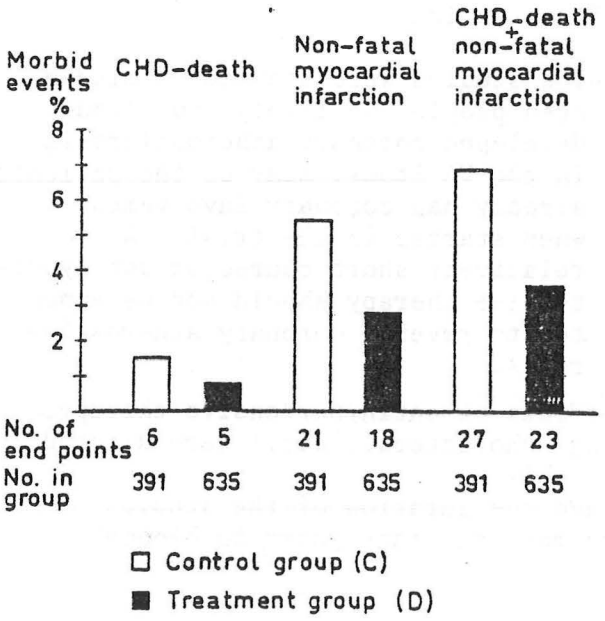


Figure 33

The effect on HDL and triglycerides

However, beta-blockers may raise serum triglycerides and lower HDL, thereby adding to risk (Helgeland *et al*, 1978; Day *et al*, 1979). The issue is complicated since other antihypertensive agents also affect lipids: serum triglyceride levels are raised and HDL levels are either unchanged (Grimm *et al*) or lowered (Gluck *et al*, 1978) by diuretics. Other adrenergic inhibitors (reserpine, Aldomet) in addition to beta-blockers may also adversely alter serum lipids (Ames and Hill, 1979). Until the issue is cleared, at least a measurement of serum triglyceride and HDL should be made prior to and a few months after institution of any antihypertensive regimen. Those patients whose triglycerides rise or HDL falls should be protected by a cholesterol-lowering diet, which will work in the face of diuretic therapy (Grimm *et al*, 1979).

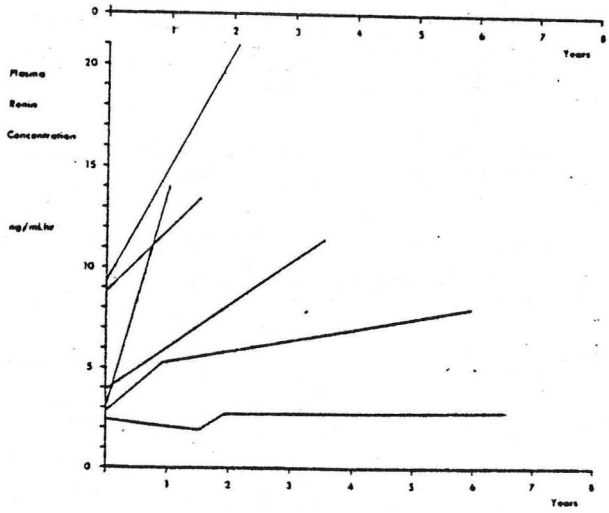
All things considered, I agree with the Editorialist in the British Medical Journal: "There seems no compelling reason to ignore the cheaper and well-tested thiazide diuretics in favour of the more costly beta-blockers in those patients with essential hypertension for whom treatment with a single agent is sufficient" (Editorial, Br Med J, 1978). Beta-blockers are attractive, particularly when only one dose a day is needed (Douglas-Jones *et al*, 1978; Millar-Craig *et al*, 1979). But about 25% of patients cannot take them because of side effects and their multiple effects may involve some that are deleterious--plasma norepinephrine levels are increased by beta-blockers (Franco-Morselli *et al*, 1978). Used by themselves, only about half of hypertensives will be controlled (VA Cooperative Study, 1977). So, overall, the stepped care approach seems best: start with a diuretic; if that doesn't work, add an adrenergic inhibitor, which for most will be a beta-blocker.

Does renin prognosticate risk?

There are then problems with all forms of antihypertensive therapy which may interfere with the desired lowering of cardiovascular risk. It would obviously be of great help to have a marker for subsequent risk beyond the present level of the pressure and the existing degree of target organ damage to decide who needs immediate therapy and who can safely be watched. We've all seen patients who seem to have mild disease who rapidly develop serious sequelae and others who seem to live forever without trouble despite very high levels of pressure.

The level of plasma renin activity (PRA) or the renin profile, based on the upright PRA and a 24-hour urine sodium, have been proposed as a guide to prognosis. The study showing that no hypertensives with low renin had heart attacks or strokes, whereas 11% of those with normal renins had one of these complications was a retrospective analysis (Brunner *et al*, 1972). A large number of subsequent retrospective analyses failed to find protection with low PRA (Kaplan, 1975).

The only *prospective* study of renin levels as prognostic indicators of CV risk offers a logical explanation of why the retrospective analysis of Brunner *et al* was probably wrong. When PRA levels were determined and patients then followed for 5 years, the number of heart attacks and strokes was just as large in those with initially low renin as in those with normal renin (Birkenhager *et al*, 1977). But when a CV event happened in a low renin patient, the renin level then usually rose (Figure 34). Thus, a retrospective study would falsely identify those previously low renin patients as having normal renins.



- Changes in plasma renin concentration after the occurrence of a myocardial infarction in 6 patients with essential hypertension.

Figure 34

Since renin levels don't help, we will have to depend upon the two tested criteria--the level of the blood pressure and the degree of target organ damage--to decide upon the need for therapy. In addition, the coexistence of additional

risk factors (Table 22) should be considered in deciding upon the need for therapy. The more the risk, the more the need for early antihypertensive therapy.

TABLE 22

Factors Associated with Definite, Probable or Possible Increase Cardiovascular Risk

Usually Subject to Modification	Not subject to modification
Hypertension	Young age
Cigarette smoking	Male sex
Hyperlipidemia	Black race
Obesity	Family history:
Hyperuricemia	a. Myocardial infarction
Sedentary lifestyle	b. Stroke
High sodium diet	c. Premature deaths
Carbohydrate intolerance	

REFERENCES: *Management of the "mild" hypertensive*

Ames R, Hill P. Increase in serum triglyceride upon adding antiadrenergic drugs to diuretics in the treatment of hypertension. Clin Res 1979; 27:540A. (abstract)

Beevers DG, Johnston J, Devine BL et al. Relation between prognosis and the blood pressure before and during treatment of hypertensive patients. Clin Sci Mol Med 1978; 55:333s-336s.

Berglund G, Sannerstedt R, Andersson O et al. Coronary heart-disease after treatment of hypertension. Lancet 1978; 1:1-5.

Birkenhager WH, Kho TL, Schalekamp MADH etal. Renin levels and cardiovascular morbidity in essential hypertension: a prospective study. Acta Clin Belgica 1977; 32:168-172.

Brunner HR, Laragh JH, Baer L et al. Essential hypertension, renin and aldosterone, heart attack and stroke. N Engl J Med 1972; 286:441-449, 1972.

Day JL, Simpson N, Metcalfe J, Page RL. Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. Br Med J 1979; 1:77-80.

Douglas-Jones AP, Baber NS, Lee A. Once daily propranolol in the treatment of mild to moderate hypertension: a dose range finding study. Europ J Clin Pharmacol 1978; 14:163-166.

Editorial. Which drug for hypertension? Br Med J 1978; :75076.

Franco-Morselli R, Baudouin-Legros M, Meyer P. Plasma adrenaline and noradrenaline in essential hypertension and after long-term treatment with beta-adrenoreceptor-blocking agents. Clin Sci Mol Med 1978; 55:97s-100s.

Gluck A, Baumgartner G, Weidmann P et al. Increased ratio between serum beta- and alpha-lipoproteins during diuretic therapy: an adverse effect? Clin Sci Mol Med 1978; 55:325s-328s.

Grimm RH, Leon A, Hunninghake D et al. Increased lipids and lipoproteins in diuretic-treated mild hypertensives. Am J Cardiol 1979; 43:419. (abstract)

Helgeland A, Hjermann I, Leren P. High density lipoprotein cholesterol and antihypertensive drugs: the Oslo study. Br Med J 1978; 2:403.

Holland OB, Nixon JV, Kuhner L. Diuretic-induced ventricular ectopic activity. Clin Res 1979; 27:314A. (abstract)

Kaplan NM. The prognostic implications of plasma renin in essential hypertension. JAMA 1975; 231:167-170.

Larbarthe DR. The cardiovascular complications of hypertension. In: Hypertension: Determinants, Complications and Interventions. ed. G Oeesti and CR Klimt. New York, Grune & Stratton, 1979, p. 126.

Miall WE, Chinn S. Blood pressure and ageing; results of a 15-17 year follow-up study in South Wales. Clin Sci Mol Med 1973; 45:23s-33s.

Millar-Craig MW, Kenny D, Mann S. Effect of once-daily atenolol on ambulatory blood pressure. Br Med J 1979; 1:237-238.

Mogensen CE. Progression of nephropathy in long-term diabetics with proteinuria and effect of initial anti-hypertensive treatment. Scand J Clin Lab Invest 1976; 36:383-388.

Mogensen CE. Diabetes and hypertension. Lancet 1979; 1:388-389.

Morgan T, Adam W, Gillies A, Carney S. Treatment of mild hypertension. Clin Sci Mol Med 1978; 55:305s-306s.

Neuvonen PJ, Pentikainen PJ, Jounela AJ. Effect of diuretic, beta-adrenoceptor blocking agent and their combination on elevated blood pressure and serum potassium: A cross-over study. Br J Clin Pharmacol 1978; 6:363-367.

Smith WM. Hypertension: who syould be treated? Resident & Staff Physician 1979; 100:3d-19d.

U.S. Public Health Service Hospitals Cooperative Study Group. Treatment of Mild Hypertension. Results of a ten-year intervention trial. Circ Res 1977; 40 (Suppl I):98-105.

Stewart IMG. Compared incidence of first myocardial infarction in hypertensive patients under treatment containing propranolol or excluding beta-receptor blockade. Clin Sci Mol Med 1976; 51:509s-511s.

Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure and prior cardiovascular disease. Further analysis of side effects. Circulation 1972; 45:991.

Veterans Administration Cooperative Study Group on Antihypertension Agents. JAMA 1977; 237:2303.

Whisnant JP, Cartlidge EF, Elveback LR. Carotid and Vertebral-basilar transient ischemic attacks: effect of anticoagulants, hypertension, and cardiac disorders on survival and stroke occurrence--a population study. An Neurol 1978; 3:107-115.

Wilhelmsen C, Vedin A, Wilhelmsen L, Tibblin G. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 1974; 2:1157-1159.

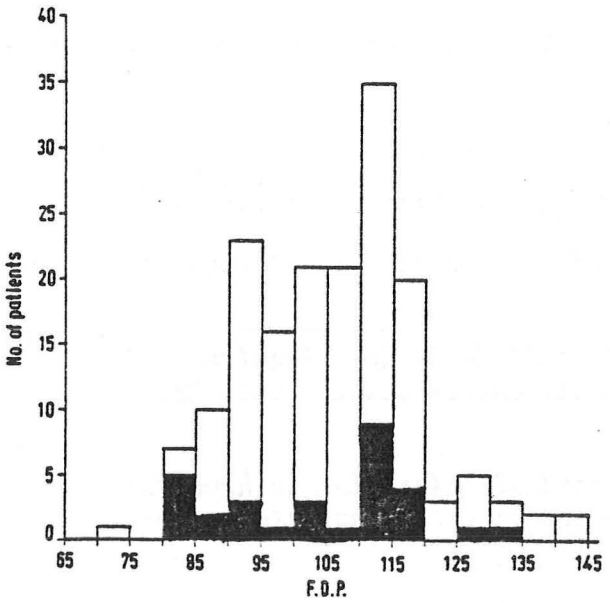
The goal of therapy

The goal of therapy is generally accepted to be a diastolic blood pressure of 90 mm Hg or less (Report of Joint National Committee, 1977). There seems little need to lower the pressure much below 90, though the life insurance actuarial data show a lower mortality with a diastolic of 80 than of 90. But recall that, in Framingham, long-term CV morbidity was not decreased further when the diastolic levels were decreased below 90.

In the VA Cooperative Study, cardiovascular morbidity was reduced almost as much in those on therapy whose diastolics could not be brought down to 90 as it was in those who were lowered to 80 or below (Taguchi and Freis, 1974) (Table 23).

A recent paper in Lancet by Dr. IMG Stewart purports to demonstrate an *increase* in myocardial infarctions among patients whose diastolics were lowered below 90 mm Hg (Stewart, 1979). The paper has a large number of major flaws and *it should not be taken as proof that effective therapy is harmful.* The flaws include these:

--the diastolic blood pressures are the fourth Kortkoff sound, so that Stewart's 90 mm Hg is about 80 mm Hg as we take the blood pressure. The excess in MI's was mainly in those with fourth phase diastolics below 85, or with fifth phase diastolics below 75 mm Hg (Figure 35). One shouldn't be surprised if such markedly low pressures were associated with tissue hypoperfusion.



-Frequency distribution of F.D.P. in 169 patients.

Open columns=patients who did not have myocardial infarct; closed columns=patients who had myocardial infarct.

Figure 35

--The patients were classified as to their levels of final diastolic pressure (FDP). But many of the FDP's were not actually measured but were "expected" to be lower or higher than the last actual measurement because more or less antihypertensive

TABLE 23

Incidence of Morbidity in Subgroups with Elevated and Normal Diastolic Blood Pressures during Treatment.

Group	4-Mo Blood Pressure*			Average of Blood Pressures†		
	No.	No. with events	% with events	No.	No. with events	% with events
Untreated, total	194	56	28.9	194	56	28.9
Treated, total	186	22	11.8	186	22	11.8
Subgroup A‡	67	10	14.9	66	8	12.1
Subgroup B	62	6	9.7	61	7	11.5

drugs had been dispensed at that visit.

--The patients were poorly selected, matched and controlled. The mean interval between blood pressure readings was 8 months.

--Patients who dropped out or who were non-compliant with therapy were included.

--The study involved patients with severe hypertension having fourth sound diastolics from 105 to 140 mm Hg, with a mean of 123.7. Yet Stewart compares his data with the results of the VA Study where the fifth phase diastolic was 90 to 115.

--Stewart makes a number of false statements, using references (his numbers 19 and 20) that do not contain the data he ascribes to them.

Not only should Stewart be faulted, but the editors of Lancet have done the world a disservice by publishing such a flawed polemic that will be used as a defence for inadequate therapy.

I believe that 90 mm Hg (fifth phase) is a reasonable goal. There seems little value in going much lower though I know of no proof that an 80 or 85 is, in fact, harmful. If a patient with an initial diastolic blood pressure of 105 happens to drop to 85 on a single, small dose of a diuretic, I see no reason to change therapy. On the other hand, it seems unnecessary to add a lot more medication onto someone who runs 90 to 95.

Can Therapy Be Stopped?

In a VA Study, involving men who started with diastolic blood pressures between 90 and 115 mm Hg, therapy was stopped in 60 patients whose diastolic blood pressure had remained below 90 for the prior two or more years. Over the next 72 months while on placebo, 15% of these previously treated mild hypertensives kept their diastolic blood pressures below 95 mm Hg (VA Study, 1975).

Three other studies have followed patients after a period of therapy:

--Of 69 patients, 23% remained normotensive for 10 to 42 months (Thurm and Smith, 1967).

--Of 65 patients, only 2 (3%) remained normotensive over an eight year follow-up (Dustan *et al*, 1968).

--Of 316 patients, only 5% remained normotensive for the next 29 to 112 months (Perry *et al*, 1966).

Thus, if patients respond very well and remain below 90 mm Hg, 5 to 20% may be expected to remain normotensive for up to 5 years if therapy is stopped. Some of this non-treatment normotension may reflect weight loss of other changes, but the hypertensive process may really be reversible after therapy. Structural thickening in resistance vessels will recede. It then may be good practice to cautiously stop therapy in patients well-controlled on little medication. The patient should be carefully followed since 80 to 95% will have their hypertension return so it may be more trouble than it's worth.

REFERENCES: *The goal of therapy; Can therapy be stopped?*

Dustan HP, Page IH, Tarazi RC, Frohlich ED. Arterial pressure responses to discontinuing antihypertensive drugs. Circulation 1968; 37:370-379.

Perry HM, Schroeder HA, Catanzaro FJ et al. Studies on the Control of hypertension. VIII. Mortality, morbidity, and remissions during twelve years of intensive therapy. Circulation 1966; 33:958-972.

Report of the Joint National Committe on Detection, Evaluation, and Treatment of High Blood Pressure. JAMA 1977;237:255.

Stewart IMG. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. Lancet 1979; 1:861-865.

Taguchi J, Freis ED. Partial reduction of blood pressure and prevention of complications in hypertension. N Engl J Med 1974; 291:329-331.

Thurm RH, Smith WM. On resetting of "barostats" in hypertensive patients. JAMA 1967; 201:85-88.

VA Cooperative Study Group on Antihypertensive Agents. Return of elevated blood pressure after withdrawal of antihypertensive drugs. Ciruclation 1975; 51:1107-1113.

GUIDES TO IMPROVING MANAGEMENT

Recognizing the costs and problems of anithypertensive therapy, attention will be given to ways to improve patient adherence to therapy and to the use of non-drug modalities which may be helpful in managing patients with no or little durg therapy.

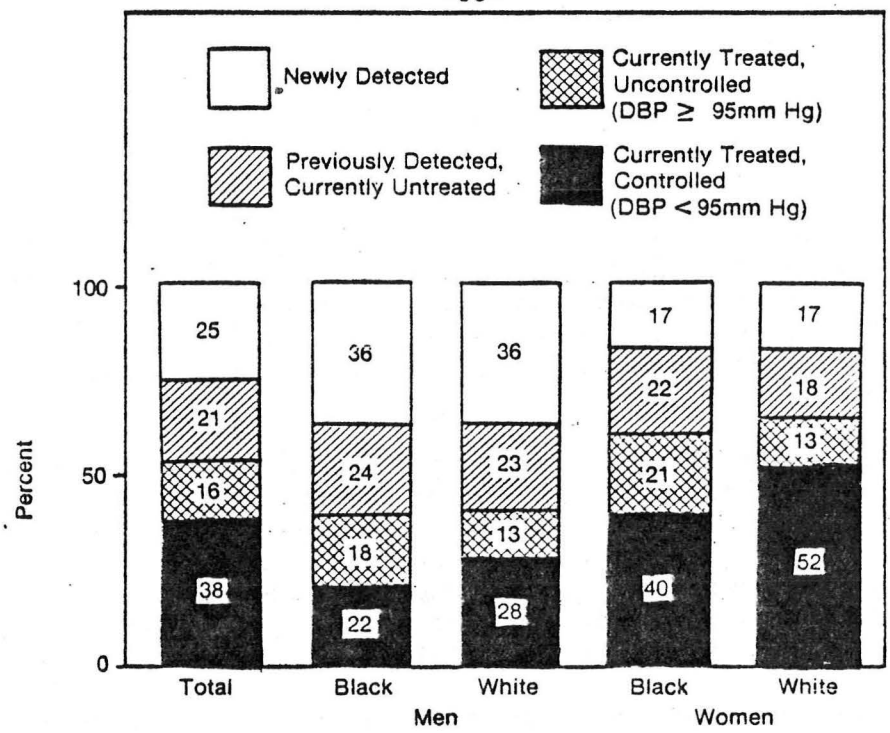
It should be noted that we are doing better: most patients have been identified and, in some areas, the majority are under good control (Berkson *et al*, 1979; Kochar *et al*, 1979).

It doesn't take special screening programs to identify most hypertensives. Since over 80% of people visit a medical practitioner each year, if the blood pressure is simply taken at each contact, most will be identified. When this is done, screening and management are greatly improved (Barber *et al*, 1979). However, there are many who remain at increased risk because they have not been identified and even more because they are not under adequate control (Figure 36) (Hypertension Detection Group, 1977).

Part of this reflects *physician* non-compliance:

--In private practitioner's offices, most patients do not have their blood pressure taken (Cypress, 1979)

--Among patients diagnosed as hypertensive under the care of board-certified internists in New York City, over half were lost to follow-up within a year and only 55% of those who remained under therapy achieved good control (Engelland *et al*, 1979).



—Status of actual hypertensives at first screen. DBP indicates diastolic blood pressure.

Figure 36

REFERENCES: *Guides to improving management*

Barber JH, Beevers DG, Fife R et al. Blood-pressure screening and supervision in general practice. Br Med J 1979; 1:843-846.

Derkson DM. Changing trends in hypertension detection and control: the Chicago experience. Am J Cardiol 1979; 43:419. (abstract)

Cypress BK. The role of ambulatory medical care in hypertension screening. Am J Public Health 1979; 69:19-24.

Engelland AL, Alderman MH, Powell HB. Blood pressure control in private practice: a case report. Am J Public Health 1979; 69:25-29.

Hypertension Detection and Follow-up Program Cooperative Group: Blood pressure studies in 14 communities. JAMA 1977; 237:2385-2391.

Ways to improve adherence to therapy

Just identifying people as hypertensive is not enough, they must be brought into an effective management program. If not, there may be disadvantages to the recognition of hypertension: among men working in a Canadian steel mill, those who were newly found to be hypertensive were referred to physicians for continued care; among those who did not start therapy, absenteeism from work rose 80% (Haynes *et al*, 1978). The increased absenteeism was not related to the severity of the disease and was not seen among those who were compliant with therapy.

Many approaches, some simple, others more complicated, have been shown to improve adherence to therapy and control of hypertension (Taylor *et al*, 1978). These include:

--Providing patients with written instructions about their medication, a personal blood pressure follow-up card and mailing appointments to those who missed a visit (Takala *et al*, 1979).

--Decreasing the number of doses and the number of pills taken daily (Haynes *et al*, 1977). Once-a-day therapy with one or two pills should be possible for most hypertensives; twice a day therapy is enough for almost all the rest.

--At the Johns Hopkins Hospital Clinics, similar in nature to Parkland's, a patient educational program improved the proportion of patients under good control from 38% to 66% while a control group receiving standard care had no change in control (Levine *et al*, 1979). The program consisted of 3 parts: 1) a 15 minute personal interview with a graduate student after a clinic visit to clarify therapy; 2) a home visit by a community aide to encourage family support; 3) a series of small-group meetings to increase patient motivation.

--At the Peter Bent Brigham Hospital, providing patients with small monetary awards and having them counselled by nurses improved compliance (Shepard *et al*, 1979).

--Home blood pressure recording is accepted by most patients (Wilkinson and Raftery, 1978) and will improve their control (Johnson *et al*, 1978).

--Patient-physician negotiation as to what each expects from the other and what each is willing to perform sounds great (Benarde and Mayerson, 1979) but most physicians are probably unwilling to take the time and trouble and to treat patients as equals (in the medical care setting).

REFERENCES: *Ways to improve adherence to therapy*

Bauer GE, Baker J, Hunyor SN, Marshall P. Side-effects of antihypertensive treatment: a placebo-controlled study. Clin Sci Mol Med 1978; 55:341s-344s.

Bernarde MA, Mayerson EW. Patient-physician negotiation. JAMA 1978; 239:1413-1415.

Haynes RB, Sackett DL, Taylor DW et al. Manipulation of the therapeutic regimen to improve compliance: conceptions and misconceptions. Clin Pharmacol Ther 1977; 22:125-130.

Haynes RB, Sackett DL, Taylor DW et al. Increased absenteeism from work after detection and labeling of hypertensive patients. N Engl J Med 1978; 299:741-744.

Johnson AL, Taylor DW, Sackett DL. Self-recording of blood pressure in the management of hypertension. Can Med Assoc J 1978; 119:1034-1039.

Levine DM, Green LW, Deeds SG et al. Health education forhypetensive patients. JAMA 1979; 241-1700-1704.

Shepard DS, Foster SB, Stason WB et al. Cost-effectiveness of interventions to improve compliance with antihypertensive therapy. Prev Med 1979; 8:229. (abstract)

Takala J, Niemela N, Rosti J, Sievers K. Improving compliance with therapeutic regimens in hypertensive patients in a community health center. Circulation 1979; 59:540-543.

Wilkinson PR, Raftery EB. Patients' attitudes to measuring their own blood pressure. Br Med J 1978; 1:824.

The use of non-drug modalitites

Even with the most highly motivated patients and with the use of all appropriate techniques to improve adherence, problems still arises with anti-hypertensive drugs. Although many complaints attributed to drugs are in fact seen just as commonly with placebo (Bulpitt *et al*, 1976), sleepiness, depression, fatigue or impotence are likely induced by therapy in as many as a third of the patients (Bauer *et al*, 1978).

To reduce the need for drug therapy and to reduce the amount if it's needed, non-drug modalities are worth trying. According to an FDA Survey taken in 1978, the majority of physicians are using them with modest success.

REFERENCES: *The use of non-drug modalities*

Bauer GE, Baker J, Hunyor SN, Marshall P. Side effects of antihypertensive treatment: a placebo-controlled study. Clin Sci Mol Med 1978; 55:341s-344s.

Bulpitt CJ, Doller CT, Carne S. Change in sysmptoms of hypertensive patients after referral to hospital clinic. Br Heart J 1976; 38:121-128.

Food and Drug Administration. Final Report: Diagnosis and Management of Hypertension. National High Blood Pressure Education Program, Bethesda, Md.

Weight reduction

Obesity is likely responsible for some hypertension--particularly in children. A special benefit may therefore accompany weight reduction--a significant fall in blood pressure. The fall may be enough that many mild hypertensives could be spared antihypertensive drug therapy.

The antihypertensive potential of weight reduction has been recognized for some time (Fletcer, 1954). Many low calorie diets are also low in sodium, which likely explains the special efficacy of the rice diet (Kempner *et al*, 1975). In a study from Israel (Reisin *et al*, 1978) 81 patients lost an average of 20 pounds in 4 months and 79 of 81 had a significant fall in blood pressure (Figure 37). The sodium intake was purposely increased in those on the diet (Groups I and IIa) so that their 24-hour urine soidum excretion was slightly higher than those who were left alone (Group IIb). Thus, the observed reduction in blood pressure must be attributed to weight loss and not sodium restriction.

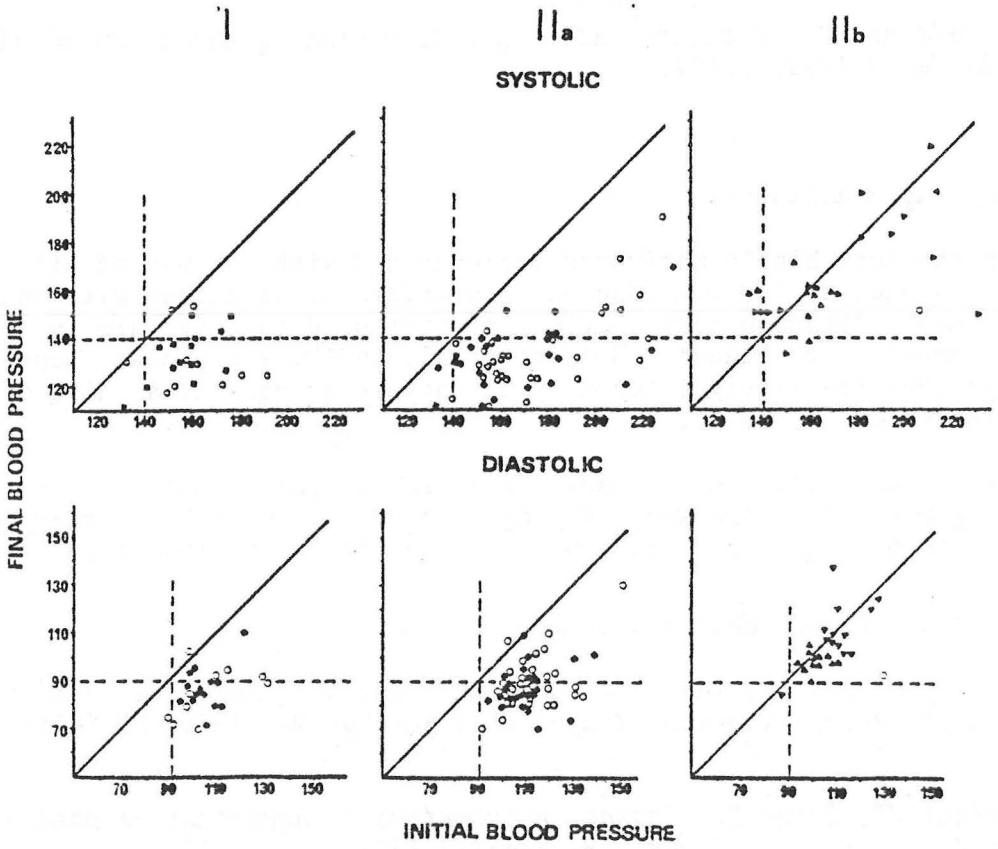


Figure 37

A dramatic fall in blood pressure may be seen whenever a stringent diet is started and that likely reflects shrinkage of fluid volume by an initial diuresis. This is seen with total starvation and 300-calorie diets (Vertes *et al*, 1979). With continued use of such low-calorie diets, part of the sustained fall in blood pressure may reflect a suppression of the renin-aldosterone mechanism (Tuck *et al*, 1979).

More gentle weight reduction of only a modest degree may lower the blood pressure. In a Chicago Prevention Evaluation Program non-pharmacologic, nutritional measures (restriction of calories and saturated fat, exercise, cessation of smoking) were able to lower the blood pressures of most of the 115 men who started off with mild hypertension (Table 24) (Stamler *et al*, 1979).

TABLE 24

CHICAGO CORONARY PREVENTION
EVALUATION PROGRAM

(Stamler, J. *et al.* in press, 1979)

Years in CPEP	No. of Men	Weight lbs	Serum Cholesterol	Systolic BP	Diastolic BP
Baseline	115	197	248	147.7	96.3
2 years	113	- 12.6	- 22.3	- 12.4	- 9.3
5 years	96	- 8.4	- 21.8	- 10.8	- 8.0
10 years	24	- 7.3	- 17.0	- 6.4	- 7.7

REFERENCES: Weight reduction

Fletcher AP. The effect of weight reduction upon the blood-pressure of obese hypertensive women. Quart J Med 1954; 23:331-345.

Kempner W, Newborg BC, Peschel RL, Skyler JS. Treatment of massive obesity with rice/reduction diet program: an analysis of 106 patients with at least a 45-kg weight loss. Arch Intern Med 1975; 135:1575-1584.

Reisin E, Abel R, Modan M et al. Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. N Engl J Med 1978; 298:1-6.

Stamler J, Farinaro E, Mojonnier LM et al. Prevention and control of hypertension by nutritional-hygienic means: Long-term experience of the Chicago coronary prevention evaluation program. Submitted for publication.

Tuck ML, Dornfield L, Kledzik G. Weight loss lowers renin and aldosterone levels in obese patients. Clin Res 1979; 27:67A. (abstract)

Vertes V, Miller SA, Dornfeld L. Effects of weight loss on blood pressure in massively obese hypertensive patients. Pre Med 1979; 8:243. (abstract).

Moderate sodium restriction

Sodium excess may be a cause of hypertension. Sodium restriction will likely improve its control. Rigidly restricted diets, such as Kempner's rice diet, will lower the blood pressure significantly (Dole *et al*, 1951). But these regimens are impractical and, with the availability of diuretics, unnecessary. However, with the advent of diuretics, many discarded the benefits of moderate sodium restriction.

The average daily sodium intake in the U.S. (as reflected in 24-hour urine sodium excretion) is around 175 mEq or 10 grams of NaCl or 4 grams of sodium. Some ingest much more, enough to totally ablate the antihypertensive effect of diuretic therapy. If the amount can be halved, to around 75 mEq/day, a slight but definite antihypertensive effect can be obtained (Table 25) (Parijs *et al*, 1973; Carney *et al*, 1975; Magnani *et al*, 1976). In addition, the decrease in sodium delivered to the distal tubular exchange site of sodium-for-potassium should reduce the amount of potassium swept into the urine. This is particularly true in the presence of diuretic therapy wherein sodium reabsorption in the more proximal portions of the tubule is blocked, so more sodium would reach the distal site. Moreover, the diuretic, by shrinking plasma volume, activates the renin-aldosterone mechanism and thereby heightens the potassium-for-sodium exchange (Figure 38).

TABLE 25

	Parijs 1973	Carney 1975	Magnani 1976
Regular diet (150-200 mEq/day)	167/113	163/106	160/101
Sodium restricted diet (50-90 mEq/day)	159/109	148/99	147/90
Regular diet + diuetic	152/106	140/94	
Sodium restricted diet + diuretic	143/101	133/93	

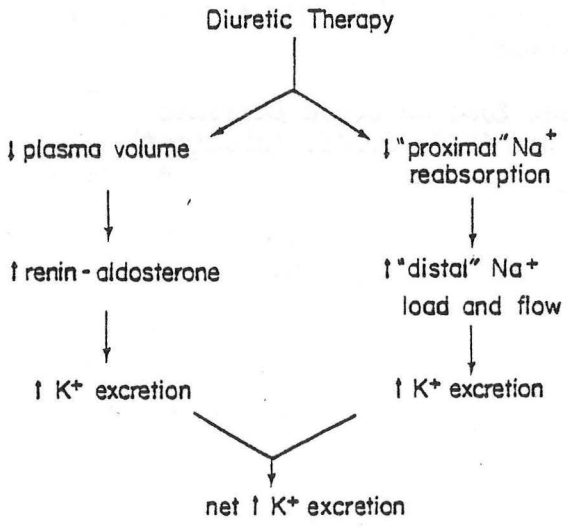


Figure 38

We have compared the amount of potassium wastage during 4 week periods of diuretic intake in the same hypertensive patients while they receive a diet either normal (175-200 mEq) or moderately restricted (75 mEq) in sodium. The amount of potassium wastage was about half as much on the lower sodium diet (Ram *et al*, 1978; Garrett & Kaplan, 1979).

If a more rigid restriction of dietary sodium is achieved, the effect on potassium wastage may be counter to that desired: with a 17 mEq a day (Landmann-Suter and Struyvenberg, 1978) or a 50 mEq a day (Von Brummelen *et al*, 1978) sodium diet, diuretic-induced potassium wastage was increased. These more rigid restrictions likely activated the renin-aldosterone system so much as to more avidly

reabsorb sodium and thereby waste more potassium. Since few patients will limit their sodium to such low levels, this undesired effect of rigid sodium restriction is unlikely to be seen very often.

How to achieve a moderately restricted diet

The problem in achieving a moderate restriction of sodium is the virtually ubiquitous presence of added sodium in foods that have been processed for longer grocery shelf life and prepared for quick delivery to the table by warming (Table 26). Knowing how to avoid high sodium-containing foods (Table 27) it's possible to choose some that are not only low in sodium but high in potassium and low in calories (Table 28). Obviously, the FDA should require that all foods be labelled with their sodium content, so we can be aware of where the salt is hidden.

Additional hints:

--some antacids are very high in sodium (e.g. Alka-Seltzer, BiSoDol, Rolaids). Others are quite low (e.g. Tums, Gelusil, Riopan).

--Patients should be asked to throw out all NaCl and try pure KCl salt substitutes, if they can tolerate the taste, or Morton's Lite Salt if they cannot. The salt substitutes not only cut out the sodium but a teaspoonful (4 grams) a day provides 60 mEq of potassium at a fraction of the cost of supplemental KCl (Sopko and Freeman, 1977). Many people find the salt substitutes bitter. Morton's Lite Salt is half NaCl, half KCl and most find it palatable (Mickelsen *et al*, 1977).

--Mothers who prepare their own baby foods should be advised not to add salt. Being addicted to

TABLE 26

SODIUM CONTENT OF SOME PROCESSED FOODS

	Amount	Sodium (mgms)
Tomato catsup (Heinz)	1 tbsp.	182
Frankfurter, beef (Oscar Mayer)	1	425
Bologna (Oscar Mayer)	2 slices	450
Tomato Juice (Del Monte)	1 cup	640
Cinnamon Rolls (Pillsbury)	1	630
Chicken noodle soup (Campbells)	10 oz.	1050
Frozen turkey dinner (Swanson)	1	1735
Pickle, dill	1 large	1928

TABLE 27

SIMILAR FOODS OF LOW OR HIGH SODIUM CONTENT

LOW	HIGH
Shredded Wheat (Nabisco), 1 mg/oz.	Corn Flakes (General Mills) 305 mg/oz.
Green Beans, fresh, 5 mg/cup	Green Beans, canned (Del Monte) 925 mg/cup
Orange Juice, 2 mg/cup	Tomato Juice, 640 mg/cup
Turkey, roasted, 70 mg/3 oz.	Turkey dinner (Swanson) 1735 mg
Ground Beef, 57 mg/3 oz.	Frankfurter, beef, 425 mg

TABLE 28

LOW CALORIE, LOW SODIUM, HIGH POTASSIUM

(less than 100 calories and 50 mg sodium, more than 200 mg (5 mEq) potassium per serving)

Artichoke	Orange
Banana	Orange juice
Broccoli	Peach
Brussel sprouts	Potato
Cantaloupe	Strawberries
Carrots	Tomato
Honeydew melon	Watermelon

salt, most mothers assume their babies want or need the salt and will add even more sodium than the amounts that were removed in the past year by baby food processors (Kerr *et al*, 1978).

REFERENCES: *Moderate sodium restriction*

Carney S, Morgan T, Wilson M, Matthews G, Roberts R. Sodium restriction and thiazide diuretics in the treatment of hypertension. Med J Aust 1975; 1:803-807.

Dole VP, Dahl LK, Cotzias GC et al. Dietary treatment of hypertension. II. Sodium depletion as related to the therapeutic effect. J Clin Invest 1951; 30:584-595.

Garrett BN and Kaplan NM. Duration of plasma renin activity suppression after withdrawal from beta adrenergic blockade. Clin Res 1979; 27:232A. (abstract)

Kerr CM, Reisinger KS, Plankey FW. Sodium concentration of homemade baby foods. Pediatrics 1978; 62:331-335.

Landmann-Suter R and Struyvenberg A. Initial potassium loss and hypokalaemia during chlorthalidone administration in patients with essential hypertension: the influence of dietary sodium restriction. Europ J Clin Invest 1978; 8:155-164.

Magnani B, Ambrosioni E, Agosta R, Racco F. Comparison of the effects of pharmacological therapy and a low-sodium diet on mild hypertension. Clin Sci Mol Med 1976; 51:625s-626s.

Mickelsen O, Makdani D, Gill JL, Frank RL. Sodium and potassium intakes and excretions of normal men consuming sodium chloride or a 1:1 mixture of sodium and potassium chlorides. Am J Clin Nutri 1977; 30:2033-2040.

Parijs J, Joossens JV et al. Moderate sodium restriction and diuretics in the treatment of hypertension. Am Heart J 1973, 85:22-34.

Ram CVS, Kaplan, NM. Diuretics and sodium restriction in the treatment of hypertension: effects on potassium wastage and blood pressure control. Circulation 1978; 57 & 58(Suppl II):164.

Sopko JA, Freeman RM. Salt substitutes as a source of potassium. JAMA 1977; 238:608-610.

Van Brummelen P, Schalekamp M, De Graeff J. Influence of sodium intake on hydrochlorothiazide-induced changes in blood pressure, serum electrolytes, renin and aldosterone in essential hypertension. Acta Med Scand 1978; 204:151-157.

Relaxation and biofeedback

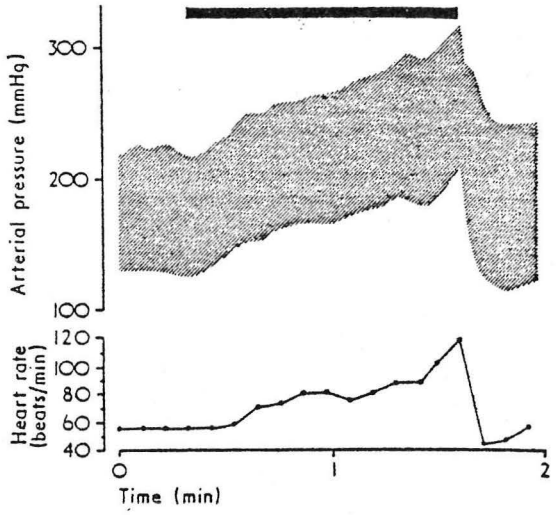
Though some find that various relaxation techniques (e.g. yoga, transcendental meditation) will lower the blood pressure (Benson, 1974) there is no good evidence that the effect lasts after the program is stopped (Shapiro *et al*, 1977). Others fail to find even a transient effect (Pollack *et al*, 1977).

Biofeedback also has its advocates (Kristt and Engel, 1975) but a controlled study showed no effect (Patel *et al*, 1978).

Exercise

Though sedentary activity may be a risk factor for CV disease, there is no clear evidence that exercise will lower the blood pressure. Small, poorly controlled studies of isotonic exercise claim significant falls in blood pressure (Boyer and Kasch, 1970; Choquette and Ferguson, 1973) but adequate studies have not been reported.

Isometric exercise will reflexely raise both systolic and diastolic pressures (Figure 39) (Ewing *et al*, 1973). Since there are no lasting cardiovascular benefits from isometric exercises, hypertensives should be asked not to do them.



Intra-arterial pressure traced from a continuous intra-arterial pressure recording in Case 7 during 50 per cent maximum voluntary contraction. The black bar indicates the duration of handgrip.

Figure 39

REFERENCES: *Relaxation, biofeedback, exercise*

Benson H. Systemic hypertension and the relaxation response. N Engl J Med 1977; 296:1152-1156.

Boyer JL, Kasch FW. Exercise therapy in hypertensive men. JAMA 1970; 211:1668-1671.

Choquette G, Ferguson RJ. Blood pressure reduction in "borderline" hypertensives following physical training. Can Med Assoc J 1973; 108:699-703.

Ewing DJ, Irving JB, Kerr F, Kirby. Static exercise in untreated systemic hypertension. Br Heart J 1973; 35:413-421.

Kristt DA, Engel BT. Learned control of blood pressure in patients with high blood pressure. Circulation 1975; 51:370-378.

Patel DJ, Frankel BL, Horwitz D et al. A ctonrol procedure for studies of blood pressure feedback in hypertension. Cardiovasc Med 1978; 3:627-630.

Pollack AA, Case DB, Weber MA. Limitations of transcendental meditation in the treatment of essential hypertension. Lancet 1977; 1:71-74.

Shapiro AP, Schwartz GE, Ferguson DCE et al. Behavioral methods in the treatment of hypertension. Ann Intern Med 1977; 86:626-636.

PREVENTION OF HYPERTENSION

Over 90% of all hypertension is essential or idiopathic. Without knowing the causes, it is obviously impossible to be certain that anything can be done to prevent the disease. However, there are strong epidemiological and experimental data incriminating obesity and excess dietary sodium intake. These seem strong enough to justify the advocacy of a reduction in calories and sodium intake, particularly in those who are genetically predisposed.

Genetic studies: The genetic contribution to blood pressure has been assessed by studies on twins, siblings, parent-child pairs, and parents versus adopted or natural children, with the conclusion that up to 60% of the population variance may be attributed to genetic differences (Feinleib, 1978). The Quebec study comparing adopted and natural children to their parents is particularly supportive of a genetic contribution (Biron, 1976). However, none of these studies exclude a major contribution from environmental influences.

Blood pressures tend to aggregate within families; children aged 2 to 14 tend to have readings that parallel their parents (Zinner *et al*, 1971), and the familial clustering persisted years later (Zinner *et al*, 1978).

In addition to supporting a genetic role, these and other studies suggest that the propensity toward hypertension may be identified relatively early in life. The relative ranking of blood pressure tends to persist in children from ages 5 to 14 over at least a 4-year period (Zinner *et al*, 1978; Webber *et al*, 1979). In Zinner's study, 57% of 88 children with initially high systolic levels remained high 4 years later and 45% of 82 with in high diastolic levels had elevated repeat measurements. In the Bogalusa study, the correlations were around 0.7 at 1 year and 0.5 at 4 years (Webber *et al*, 1979). When pressures were measured by Doppler ultrasound in even younger children, correlations were 0.38 for systolic and 0.34 for diastolic pressures, between 6 months and 1 year of age (Levine *et al*, 1978); for children between 2 and 5 years of age, the correlation was 0.55; for those between 15 and 17, it increased to 0.75 (Jesse *et al*, 1976). Others have not found such good predictability, noting greater individual variablity (Clarke *et al*, 1976).

Adequate long-time tracking data are not yet available but, as of now, it is reasonably certain that children of hypertensive parents are at greater risk and they may show a propensity toward higher blood pressures very early in childhood. Therefore, some can be identified and attempts at prevention can be contemplated.

In addition to higher blood pressure levels, children of hypertensive parents have lower urinary kallikrein excretion (Zinner *et al*, 1978). Adult blacks, both normotensive and hypertensive, excrete less kallikrein than whites (Holland & Chud, 1979). In black boys in Bogalusa, those with higher pressures have lower levels of plasma renin activity (Berenson *et al*, 1979). Hopefully, other markers of genetic predisposition will be discovered so intervention trials maybe conducted in those who are genetically susceptible.

Obesity in childhood: Children who grow faster have higher blood pressures. The rise in pressure is proportional to lean body mass and total body mass (Voors *et al*, 1977). Those who become obese tend to have higher blood pressures (Londe *et al*, 1971; Stine *et al*, 1975; Court *et al*; Voors *et al*, 1977; Rames

et al, 1978), and there is an association between skinfold thickness and hypertension (Stine *et al*, 1975). About half of hypertensive children are obese (Lieberman, 1978). If both parents are overweight and hypertensive, the probability of both obesity and higher blood pressures in their children is markedly increased. Moreover, when obese hypertensive children lose their excess weight, they may lower their blood pressure to normal (Court *et al*, 1974; Rames *et al*, 1978).

Obesity in adults: Fat people have more hypertension: in a recent screening of over 1 million people, overweight persons had from 50 to 300% more hypertension particularly if there is also a positive family history (Table 29) (Stamler *et al*, 1978). Though part of the association could reflect the recording of falsely high readings by the use of small sphygmomanometer cuffs, it holds with use of appropriate equipment (Kannel *et al*, 1967).

The blood pressure in adults tends to rise as weight is gained. Long-term, longitudinal studies in Framingham (Kannel *et al*, 1967), Evans County (Johnson *et al*, 1975), and Manitoba (Hsu *et al*, 1977) show strong correlations between gain in weight and rise in blood pressure.

The potential for preventing hypertension is an additional reason to limit over-feeding among infants and to stress prevention of excess weight gain in all age groups. Evidence that weight loss will lower the blood pressure is presented in the secton on Obesity.

Excess dietary sodium in childhood: No correlation has been found between children's blood pressure and their sodium intake (Report, 1974) or their taste threshold for salt (Lauer *et al*, 1976). However, it may very well be that all American infants are given excess dietary sodium, almost from birth, leading to a uniform preference for sodium which persists throughout life and, in those who are genetically susceptible, induces hypertension. The failure to find a difference in sodium intake between hypertensives and normotensives likely reflects a super-threshold intake by everyone--presumably those not genetically predisposed won't develop hypertension regardless of how much salt they ingest. But the critical question is: Can hypertension be prevented in those who are genetically predisposed by life-long reduction in their sodium intake?

TABLE 29

Family History	Age, yr 20-39	40-64
Normal weight		
Positive history	82.8	309.4
Negative history	46.7	118.7
Prevalence ratio	1.84	2.02
Overweight		
Positive history	182.4	443.5
Negative History	118.2	293.2
Prevalence ratio	1.66	1.92

(From Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH, JAMA 241:44, 1978.)

The answer is unknown and it may not be possible to do the study needed to provide the answer. However, certain facts are known:

1. Metabolic needs for sodium in healthy growing infants are very small (about 4 to 8 mEq per day) which is provided nicely by breast milk which contains about 7 mEq of sodium per liter.

2. American infants, being fed the usual mixed diet of milk, baby food, and table food, have been ingesting far more sodium

than needed--in the range of 38 mEq/day at 8 months and 63 mEq/day at 12 months (Report, 1974).

3. Salt preference is learned. In those societies wherein dietary sodium is sharply limited in infancy, sodium intake remains low throughout adult life even when more sodium is available.

In response to these facts and the circumstantial evidence linking sodium with hypertension, the major processors of baby foods have sharply reduce their sodium content. But mothers, unaware of the evidence, who make homemade foods for their infants add even more sodium (up to 10 times more) than was present in the processed foods before the salt restriction (Kerr *et al*, 1978) (Table 30). Thus, mothers need to be informed that their infants don't need extra sodium and that it may be harmful. There are no known hazards of lifelong sodium restriction. The evidence favoring the potential of preventing hypertension seems strong enough to make the effort worthwhile. Hopefully, people whose sodium intake was limited during infancy will have a lesser preference for sodium when they become adults.

TABLE 30

SODIUM CONTENT (mg/100 gm)

FOOD	*Beechnut/Heinz*	*Gerber*	*Homemade*
Peas	16	129	145
Corn	20	101	215
Green beans	6	107	197
Chicken	41	170	242
Beef	51	182	156

(*from* Kerr, et al: Pediatrics 62:331, 1978)

Other related factors: A positive correlation has been noted between pulse rate and blood pressure in children (Miller & Shekelle, 1976; Holland and Beresford, 1975). In addition to weight, height is also a determinant (Voors *et al*, 1977). Though some fail to find an association with the area of residence, adolescents living in inner city Cincinatti had higher pressures than economically matched adolescents living in the suburbs (Burns, 1979). Variables which don't seem related include socio-economic status, family size, and birth order. In most studies black children compared to white children of comparable size and maturity do *not* have higher levels of blood pressure, even though among black adults hypertension is about twice as frequent as among white adults. By the late teens, the racial difference may be seen. Among 18-and 19-year-olds in New York City, diastolic levels were elevated above 90 mm Hg in 24% of blacks compared to 5% of Puerto Ricans and 3% of whites (Kilcoyne, 1974).

In summary, children appear to be more likely to have higher blood pressures if their parents are hypertensive, if they are obese, if they have fast pulses, and if they excrete lower amounts of urinary kallikrein. The data are inadequate to validate any or all of these as accurate predictors of eventual hypertension. However, preliminary data show that, at least over 4 years, most blood pressures remain in the same track. Though they may still be premature, attempts at

intervention with restriction of dietary sodium and prevention of obesity seem appropriate.

REFERENCES: *Prevention of hypertension*

Berenson GS, Voors AW, Dalferes ER, Jr., Webber LS, Shuler SE. Creatinine clearance, electrolytes, and plasma renin activity related to the blood pressure of white and black children--the Bogalusa heart study. J Lab Clin Med 1979; 93:535-548.

Biron P, Moneau JG, Bertrand D. Familial aggregation of blood pressure in 558 adopted children. Can Med Assoc J 1976; 115:773-774.

Burns M, Morrison J. Prevalence of adolescent hypertension in students attending an inner city high school as compated to students attending a suburban high school. Prev Med 1979; 8:140.

Clarke W, Woolson R, Schrott H, Wiebe D, Lauer R. Tracking of blood pressure, serum lipids, and obesity in children: the Muscatine study. Circulation 1976; 54(Suppl II):11-23, 1976. (abstract)

Court JM, Hill CJ, Dunlop M, Boulton TJC. Hypertension in childhood obesity. Aust Paediatr J 1974; 10:296-300.

Feinleib M. Genetics and familial aggregation of blood pressure. In: Hypertension: Determinants, Complications and Interventions. ed Onesti G, Klimt R. New York: Grune & Stratton, 1978.

Holland OB, Chud JM. Urinary kallikrein excretion in essential and mineralocorticoid hypertension. Submitted for publication.

Hsu PH, Mathewson FAL, Rabkin SW. Blood pressure and body mass index patterns--a longitudinal study. J Chron Dis 1977; 30:93-113.

Johnson AL, Cornoni JC, Cassel JC, Tyroler HA, Heyden S, Hames CG. Influence of race, sex and weight on blood pressure behavior in young adults. Amer J Cardiol 1975; 35:523-530.

Kannel WB, Brand N, Skinner JJ, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension. The Framingham study. Annn Intern Med 1967; 67:48-49.

Kerr CM, Jr., Reisinger KS, Plankey FW. Sodium concentration of homemade bady foods. Pediatrics 1978; 62:331-335.

Kilcoyne MM, Richter RW, Alsup PA. Adolescent hypertension. I. Detection and prevalence. Circulation 1974; 50:758-764.

Levine RS, Hennekens CH, Klein B et al. Tracking correlations of blood pressure levels in infancy. Pediatrics 1978; 61:121-125. (letter to the editor)

Lieberman E. Hypertension in childhood and adolescence. In: Clinical Hyper tension. ed Kaplan NM. Baltimore: Williams & Wilkins, 1978:366.

Londe S, Bourgoignie JJ, Robson AM, Goldring D. Hypertension in apprently normal children. J Pediatr 1971; 78:569-577.

Rames LK, Clarke WR, Connor WE, Reiter MA, Lauer RM. Normal blood pressures and the evaluation of sustained blood pressure elevation in childhood: the Muscatine study. Pediatrics 1978; 61:245-251.

Stamler R, Stamler J, Riedlinger WF et al. Weight and blood pressure: findings in hypertension screening of 1 million Americans. JAMA 1978; 240:1607-1610.

Stine OC, Hepner R, Greenstreet R. Correlation of blood pressure with skinfold thickness and protein levels. Amer J Dis Child 1975; 130:905-911.

Voors AW, Webber LS, Frerichs RR, Berenson GS. Body weight and body mass as determinants of basal blood pressure in children--the Bogalusa heart study. Am J Epidemiol 1977; 106:101-108.

Webber LS, Voors AW, Berenson GS. A remarkable tracking of blood pressure in children--the Bogalusa heart study. Abstracts, Conference on CVD Epidemiology, New Orleans, March 19-21, 1979, p. 51.

Zinner SH, Levy PS, Kass EH. Familial aggregation of blood pressure rank in childhood. N Engl J Med 1971; 284:401-404.

Zinner SH, Margolius HS, Rosner B, Kass EH: Stability of blood pressure rank and urinary kallikrein concentration in childhood: an eight-year follow-up. Circulation 1978; 58:908-915.

Excess dietary sodium in adults

In addition to the previously provided support for excess sodium intake in childhood as a possible causal factor for hypertension, there are additional pieces of circumstantial evidence that incriminate continued excess sodium intake as being involved in adult hypertension (Freis, 1976):

1) Among people who ingest very little sodium, hypertension is uncommon and the "expected" rise in blood pressure with aging does not occur (Page *et al*, 1974; Oliver *et al*, 1975) (Table 31). When dietary sodium is low, potassium intake is high and that too may be important (Meneely and Battarbee, 1976).

TABLE 31

BLOOD PRESSURES IN YANOMAMO INDIANS
(*Oliver et al: Circulation 52:146, 1976*)

Average Urine Na^+ = 1.3 mEq/24 hours

Age	Males	Females
20-29	108/69	100/63
30-39	105/69	99/63
40-49	107/67	98/62
50+	100/64	106/64

There are lots of differences beyond sodium and potassium intake which may explain the differences in blood pressure. But the association between sodium intake and blood pressure is strong (Figure 40).

2. In animals who are genetically predisposed, increased sodium intake raises the blood pressure. The earlier in life the extra salt is given, the greater the rise in pressure (Dahl *et al*, 1972). Presumably this is the situation in people as well: both the genetic predisposition and the high sodium load are needed for hypertension to develop.

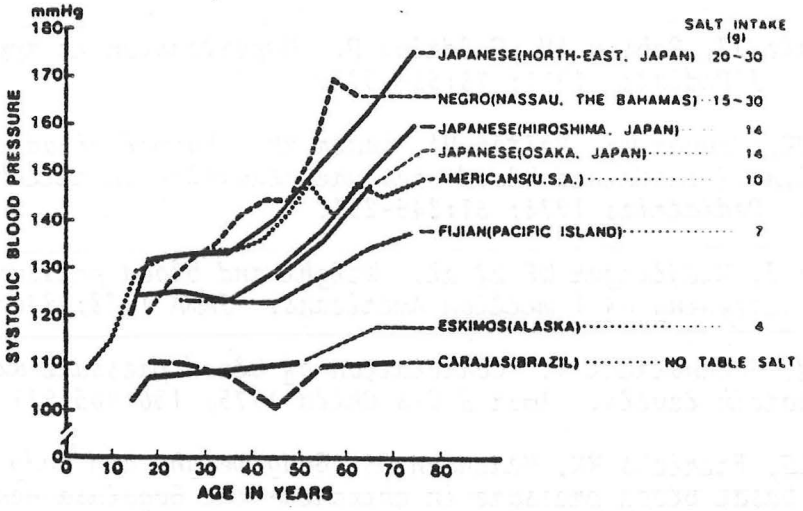


Figure 40

3. High sodium intake increases vascular resistance and pressor responsiveness to angiotensin. A specific cellular mechanism has been shown whereby increased sodium could increase intracellular ionized calcium and thereby smooth muscle contraction (Blaustein, 1977). In addition, increased sodium intake may increase protein synthesis within vascular smooth muscle cells (Friedman, 1979).

4. Years ago, Tobian and Binion (1952) reported an increase in the sodium content within arteries from hypertensive patients and animals. The red cells of essential hypertensive patients have an abnormally low Na^+/K^+ flux ratio (Garay and Meyer, 1979); if the same defect is present in vascular smooth muscle cells it could be responsible for intracellular sodium accumlation.

5. Decreasing dietary sodium intake will lower the blood pressure. The virtual absence of sodium is the reason that Kempner's rice diet is so successful in reducing the blood pressure (Kempner, 1948, Corcoran *et al*, 1951). Though he is still able to convince patients to eat only 3 bowls of rice a day (and pay good money for the privilege), the rest of the world finds this approach impractical. More moderate reduction in dietary sodium will lead to more moderate lowering of the blood pressure (Table 25) and this benefit can be achieved by most patients given proper instruction and motivation.

Since there is no known ill-effect of lowered sodium intake, it seems to be an eminently practical and sensible step, hopefully to prevent hypertension or at least to slow its progress.

REFERENCES: *Excess dietary sodium in adults*

Blaustein MP. Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis. Am J Physiol 1977; 232:C165-C173.

Corcoran AC, Taylor RD, Page IH. Controlled observations on the effect of low sodium dietotherapy in essential hypertension. Circulation 1951; 3:1-16.

Dahl LK. Salt and hypertension. Am J Clin Nutri 1972; 25:231-244.

Freis ED. Salt, Volume and the prevention of hypertension. Circulation 1976; 53:589-595.

Friedman SM. Sodium in blood vessels. Blood Vessels 1979; 16:2-16.

Garay RP, Meyer P. A new test showing abnormal net Na^+ and K^+ fluxes in erythrocytes of essential hypertensive patients. Lancet 1:349-353.

Kempner W. Treatment of hypertensive vascular disease with rice diet. Am J Med 1948; 4:545-577.

Meneely GR, Battarbee HD. High sodium-low potassium environment and hypertension. Am J Cardiol 1976; 38:768-785.

Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "No-salt" culture. Circulation 1975; 52:146-151.

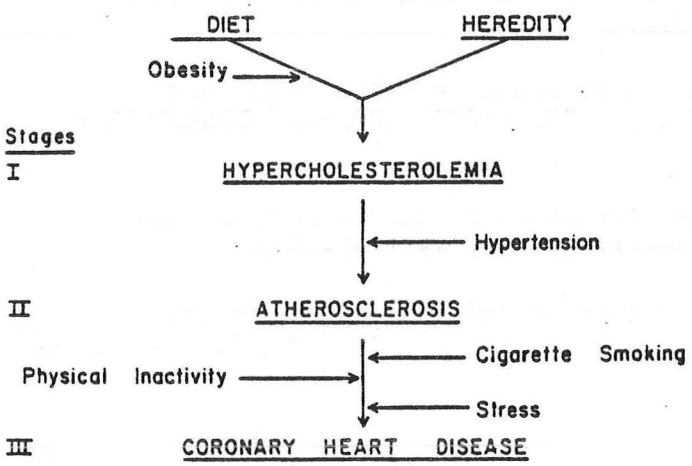
Page LB, Damon A, Moellering RC Jr. Antecedents of cardiovascular disease in six Solomon Island societies. Circulation 1974; 49:1132-1146.

Tobian L, Binion JT. Tissue cations and water in arterial hypertension. Circulation 1952; 5:754-758.

LIPID ABNORMALITIES

Considerable experimental and epidemiological evidence support a causal role of high cholesterol and triglycerides in premature atherosclerosis. The "Lipid Hypothesis" or the "Diet-Heart Model" (Figure 41) has been in vogue for the past 20 years and puts cholesterol in the predominant role (Connor & Connor, 1972; Davignon, 1978; Stamler, 1978). Everyone agrees that multiple other factors are also involved either in a subsidiary manner (Figure 41) or in a complementary manner (Figure 42).

Figure 41

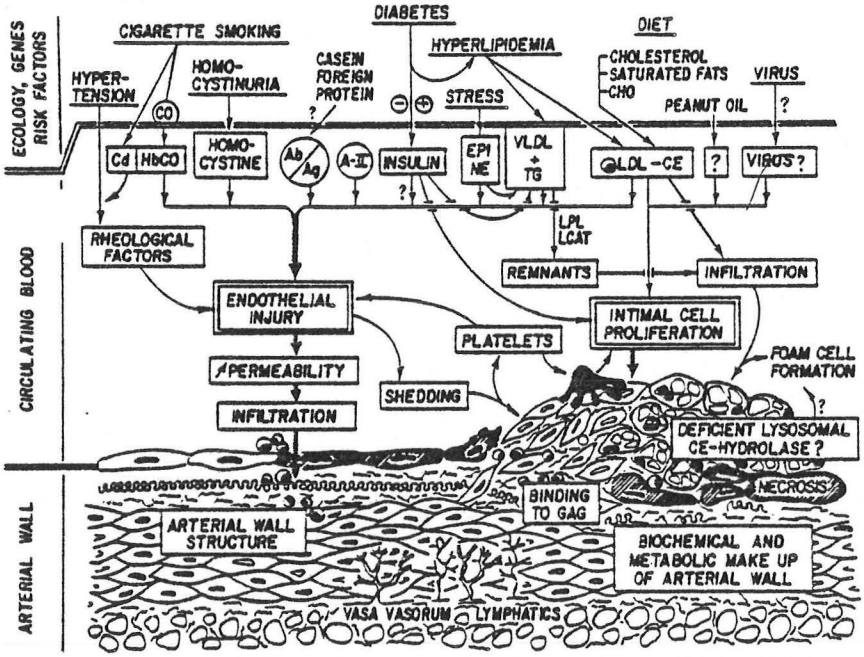


But in the past few years, voices of doubt, disbelief, and outright rejection of the Lipid Model have been heard (Ahrens, 1976; Mann, 1977; Reiser, 1978; McMichael, 1979). This presentation will present neither these opposing views nor the rebuttals in defense of the Lipid Model (Glueck *et al*, 1978; Glueck and Connor, 1978). I believe the evidence of a relationship is reasonably convincing though a causal connection has not been proved and there is still no convincing evidence that therapy of lipid abnormalities will overcome the increased risk which attends them.

BACKGROUND

Before going further, a few explanatory diagrams should be helpful. Table 32 shows some of the physical properties of

Figure 42



-Multifactorial interactions in atherogenesis. Three levels of influence are depicted: ecological and genetic factors, intermediates in circulating blood, and arterial wall components. Endothelial injury and intimal cell proliferation are emphasized as key elements in atherogenic process. CHO indicates carbohydrates; Ab/Ag, immune complexes; A-II, angiotensin II; EPI, epinephrine; NE, norepinephrine; VLDL, very-low-density lipoproteins; LDL, low-density lipoproteins; TG, triglycerides; CE, cholesteryl esters; LPL, lipoprotein lipase; LCAT, lecithin/cholesterol acyltransferase; and GAG, glycosaminoglycans (from Davignon').

the various lipoproteins (Brunzell *et al*, 1978); Table 33 more about their composition; and Table 34 relates the various lipoproteins to the Fredrickson typing which is used in some places (Glueck & Kwiterovich, 1978). The dynamic relationships between these various lipoproteins, remnants and organs are shown in Figure 43 (Sodhi & Mason,1978).

TABLE 32

	Ultracentrifugal			
Physiologic	Term	Flotation Rate S_f	Density	Electrophoretic
Chylomicron	Chylomicron	>400		Origin
Endogenous VLDL	VLDL	400	<1.006	Pre-Beta
Remnant Lipoproteins	IDL (LDL_1)	20	1.006–1.019	Broad Beta
LDL	LDL (LDL_2)	12	1.019–1.063	Beta
HDL	HDL	0	1.063–1.25	Alpha

VLDL—very low density lipoprotein.
IDL—intermediate density lipoprotein (originally classified as part of LDL).
LDL—low density lipoprotein.
HDL—high density lipoprotein.

TABLE 33

—Classification and Properties of the Major Human Plasma Lipoproteins				
	Chylomicrons	Very-Low-Density Lipoproteins	Low-Density Lipoproteins	High-Density Lipoproteins
Migration on paper electrophoresis	Origin	Prebeta	Beta	Alpha
Density ranges (gm/ml), ultracentrifuge	<0.95	0.95-1.006	1.006-1.063	1.063-1.21
Average composition				
Protein	2	8	21	50
Cholesterol	7	20	45	22
Triglyceride	84	51	11	4
Phospholipid	7	19	22	24
Protein components (apolipoproteins)				
Major	ApoC-I, II, & III	ApoC-I, II, & III	ApoB	ApoA-I & ApoA-II
Minor	ApoA-I, II, & ApoB	Arginine-rich polypeptide	ApoC-I, II, & III	ApoC-I, II, III, & ApoD

TABLE 34

-Classification of Hyperlipidemia According to Plasma Lipoprotein Pattern*			
Fredrickson Type	Lipids†	Lipoproteins	Appearance of Plasma‡
I	C high; TG > 1,000 mg/100 ml	Chylomicrons greatly increased	Thick, creamy layer over clear infranant
IIa	C high; TG normal	LDL increased	Clear
IIb	C high; TG high	LDL & VLDL increased	Slightly cloudy to turbid
III	C high; TG high	VLDL with prebeta mobility & abnormal C/TG ratio	Cloudy to milky (rarely, cream layer)
IV	C normal or high; TG high	VLDL increased, LDL normal	Slightly cloudy to turbid
V	C high; TG > 1,000 mg/100 ml	Chylomicrons & VLDL increased	Thick, creamy layer over turbid infranant

*C indicates cholesterol; TG, triglycerides; LDL, low-density (beta) lipoproteins; and VLDL, very-low-density (prebeta) lipoproteins.
†Criteria of abnormality are those presented for group A in Table 1.
‡Assumes that plasma was obtained from fasting patient and stored at 4 C overnight.

The distribution of total cholesterol and the three lipoprotein components in a random population of 3,581 males and 3,426 females studied in 10 Lipid Research Clinics across the U.S. (Figure 44) shows one reason why women are at lesser CV risk, at least before the menopause (Rifkin *et al*, 1979). Notice their lower total cholesterol and higher HDL levels.

The risks for premature cardiovascular disease covered here do not relate to the hereditary hyperlipidemias which are involved in a considerable fraction of patients who have a myocardial infarction before age 60 but which are relatively rare in the general population (Table 35) (Goldstein *et al*, 1973). These flagrant defects have provided useful models for study of basic physiology. Certainly any patient with early coronary disease should be tested and, if one of these is discovered, the entire family screened.

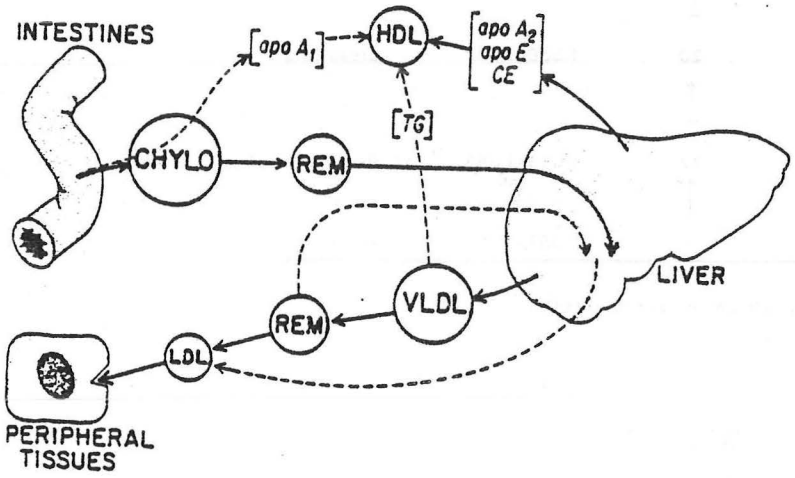


Figure 43

Figure 44 →

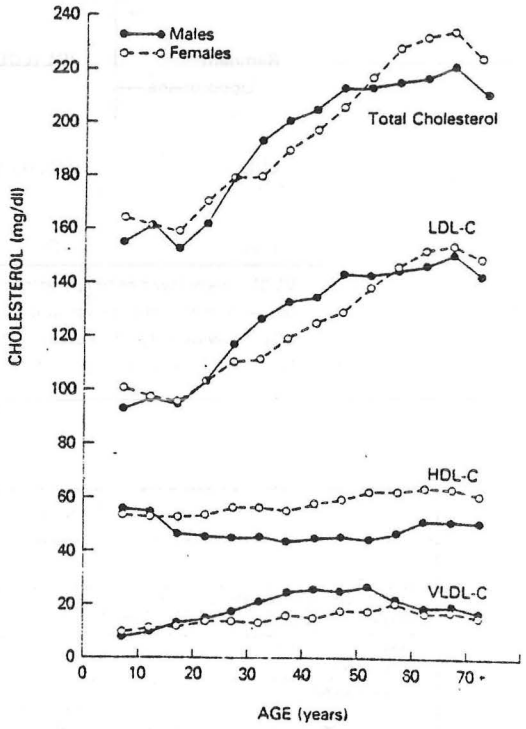


TABLE 35

Frequency of hyperlipidemia

Disorder	Myocardial infarction survivors <Age 60 (a) %	Myocardial infarction survivors ≥Age 60 (b) %	Ratio a/b	General population (%)
I Monogenic hyperlipidemia, FH	4.1	0.7	5.9	~0.1–0.2
Familial hypertriglyceridemia	5.2	2.7	1.9	~0.2–0.3
Combined hyperlipidemia	11.3	4.1	2.8	~0.3–0.5
Total	20.6	7.5	—	~0.6–1.0
II Polygenic hypercholesterolemia	5.5	5.5	1.0	—
III Sporadic hypertriglyceridemia	5.8	6.9	0.8	—

REFERENCES: Lipid Adnormalities, background

Ahrens EH. The management of hyperlipidemia: whether, rather than how. Ann Lintern Med; 1976; 85:87-93.

Brunzell JD, Chait A, Bierman EL. Pathophysiology of lipoprotein transport. Metabolism 1978; 27:1109-1127.

Connor WE, Connor SL. The key role of nutritional factors in the prevention of coronary heart disease. Prev Med 1972; 1:49-83.

Davignon J. The lipid hypothesis: pathophysiological basis. Arch Surg 1978; 113:28-34.

Glueck CJ, Mattson F, Bierman EL. Diet and coronary heart disease: another view. N Engl J Med 1978; 298:1471-1474.

Glueck CJ, Connor WE. Diet-coronary heart disease relationships reconnoitered. Am J Clin Nutri 1978; 31:727-737.

Glueck CJ, Kwiterovich PO. The lipid hypothesis: genetic basis. Arch Surg 1978; 113:35-41.

Goldstein JL, Hazzard WR, Schrott JG, et al. Hyperlipidemia in coronary heart disease: I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest 1973; 52:1533-1577.

Mann CV. Diet-Heart: end of an era. N Engl J Med 1977; 12:644-450.

McMichael J. Fats and atheroma: an inquest. Brit Med J 1979; 1:173-175.

Reiser R. Oversimplification of diet: coronary heart disease relationships and exaggerated diet recommendations. Am J Clin Nutri 1978; 31:865-875.

Rifkind BM, Tamir I, Heiss G, Wallace RB, Tyroler HA. Distribution of high density and other lipoproteins in selected LRC prevalence study populations: a brief survey. Lipids 1979; 14:105-112.

Stamler J. Lifestyles, major risk factors, proof and public policy. Circulation 1978; 58:3-19.

THE RISKS OF HYPERLIPIDEMIA

As we shall see, increased total cholesterol, increased triglycerides, and decreased HDL-cholesterol have all been found to be related to risk for premature cardiovascular disease. The relative strengths of these 3 is found to vary in different population surveys; the negative HDL relation seems the strongest (Table 36).

Hypercholesterolemia: Data such as those from the 5 studies included in the Pooling Project (Table 37) (Pooling Project, 1978) show that the relative risk for moderately elevated cholesterol is not as great as was noticed with fewer data over shorter intervals (Keys *et al*, 1972) (Figure 45). Nonetheless, a serum cholesterol over 240 mg% adds a significant risk for coronary disease. As shown in Figure 44, the mean serum cholesterol for the "normal" adult U.S. population is above 200, close to 220 in men. About 30% of normal people over 40 have an elevated serum cholesterol.

The question has been asked--are the relatively high cholesterols of the U.S. population "normal" or do they reflect a heavily diseased people who are thereby at greater risk for CV disease. The frequency distributions of serum cholesterol in the populations of South Japan, where coronary disease is rare, and East Finland, where it is rampant, reflect the problem (Figure 46). According to usual methods of establishing "normal" values in a population, a low cholesterol in Finland would be high in Japan.

In Framingham, within the presumably normal range of serum cholesterol accepted by some (180 to 310 mg%), risk for cardiovascular disease mounts over a five-fold range (Kannel *et al*, 1979). The strength of the association wanes progressively with advancing age, so that serum total cholesterol is no longer a predictor of risk in men beyond age 65.

TABLE 36

Discriminant analysis of CHD cases versus noncases among persons 50–69, using specified lipids[a]

	Bivariate standardized coefficients			Multivariate standardized coefficients			
	Cholesterol			Cholesterol			
Study group	HDL	LDL	Triglyceride	HDL	LDL	Triglyceride	No. of cases
Men							
Albany	−0.19[b]	0.20[b]	0.16[b]	−0.14	0.21[c]	0.13	151
Framingham	−0.37[c]	0.06	0.29[c]	−0.30[c]	0.09	0.20[b]	122
Honolulu	−0.30[c]	0.95[c]	0.06	−0.28[c]	0.32[c]	0.06	251
San Francisco	−0.09	0.29	0.45[b]	0.17	0.43[b]	0.61[c]	23
Evans County, white	−0.68[c]	0.59[b]	0.56[b]	−0.39	0.74[c]	0.74[c]	28
Pooled random sample	−0.24[c]	0.20[c]	0.11[b]	−0.21[c]	0.22[c]	0.09	383
Women							
Framingham	−0.26[b]	0.29[b]	0.39[c]	−0.09	0.22[b]	0.32[b]	67

[a] The Cooperative Lipoprotein Phenotyping Study. This table is taken from Castelli et al. (28) and is used with permission of the American Heart Association, Inc.

[b] $p < 0.05$.

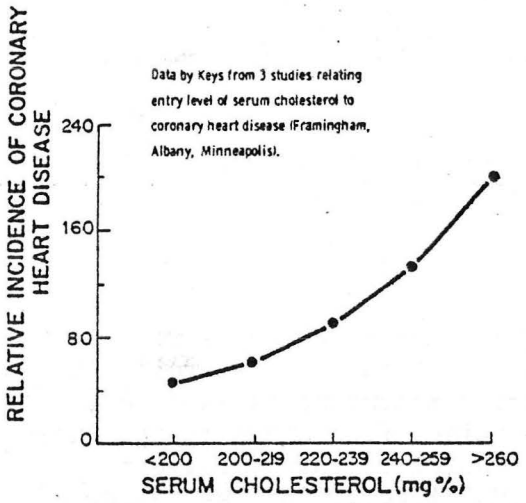
[c] $p < 0.01$.

Bivariate includes age and specified lipids; multivariate includes age and the three lipids.

TABLE 37

Serum cholesterol and risk of a first major coronary event between ages 40–64, 8,274 white men, pool 5, National Cooperative Pooling Project (final report)

Quintile of serum cholesterol and level (mg/dl)		Number of first events	Risk of an event, age 40–64, per 1,000 men	Relative risk	Absolute excess risk, per 1,000 men	Percent of all excess risk
I + II	≤ 218	166	162.7	1.00	—	—
I	≤ 194	86	172.4	—	—	—
II	194–218	80	153.0	—	—	—
III	218–240	104	186.8	1.15	24.1	8.3%
IV	240–268	167	266.3	1.64	103.6	35.8%
V	> 268	210	324.1	1.99	161.4	55.8%
All		647	222.4	—	—	—



Relative incidence rate of coronary heart disease of U.S. white men classified by entry level of serum cholesterol.

Figure 45

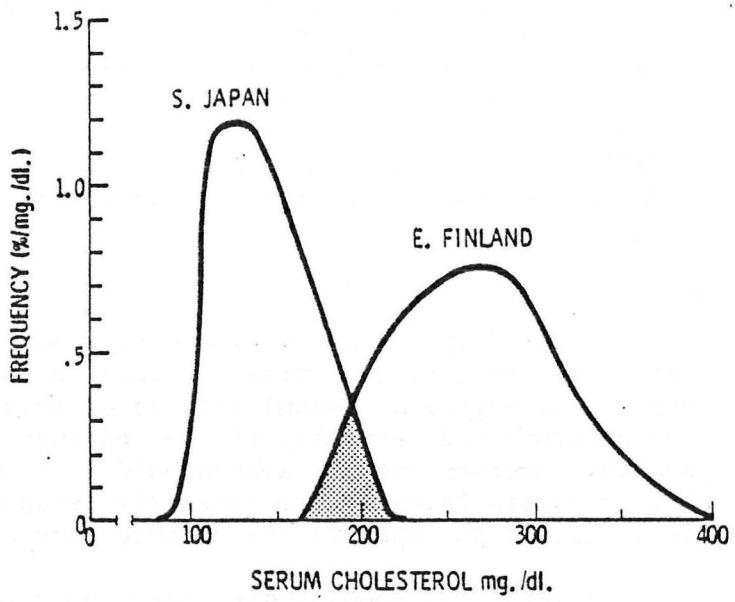


Figure 46

As we shall see, the HDL-cholesterol fraction has been found to be a much stronger predictor. But before discarding the total cholesterol or its major fraction, LDL-cholesterol, as a physiological and laboratory risk, remember these facts (Steinberg, 1978):

1. Experimental atherosclerosis can be induced solely by raising LDL levels.

2. Tissue evidence is available for a direct involvement of LDL in atherogenesis.

3. Patients with very high LDL (e.g., homozygous familial hypercholesterolemia) have markedly accelerated atherosclerosis whereas patients with almost no HDL (e.g., Tangier disease) don't have such susceptibility.

4. Lowering LDL by diet likely reduces the risk of CV disease; no data showing protection by raising HDL are available.

REFERENCES: *Hypercholesterolemia*

Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. Ann Intern Med 1979; 90:85-91.

Keys A, Aravanis C, Blackburn H, Van Buchem FSP et al. Probability of middle-aged men developing coronary heart disease in five years. Circulation 1972; 45:815-828.

Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chron Dis 1978; 31:201-306.

Steinberg D. The rediscovery of high density lipoprotein: a negative risk factor in atherosclerosis. Europ J Clin Invest 1978; 8:107-109.

Hypertriglyceridemia: The data supporting an independent risk role for increased total triglycerides is less solid than for total cholesterol. The problem is partially technical: total triglyceride measurements include chylomicrons (particularly if the specimen is obtained from a non-fasted subject) and chylomicrons are not atherogenic. Another problem is that triglyceride levels physiologically are inversely related to HDL levels, thereby making it difficult to separate the contribution of each to risk.

At least two good studies have shown that triglycerides do serve as an independent risk factor (Carlson & Bottiger, 1972; Pelkonen *et al*, 1977). Moreover in Goldstein's Seattle study of MI survivors below age 60, the incidence of hypertriglyceridemia alone was 15% whereas the incidence of hypercholesterolemia alone was only 7.6%.

REFERENCES: *Hypertriglyceridemia*

Carlson LA, Bottiger LE. Ischemic heart-disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm Prospective Study. Lancet 1972; 1:865.

Goldstein JL et al. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest 1973; 52:1533.

Pelkonen R, Nikkila EA, Koskinen S et al. Association of serum lipids and obesity with cardiovascular mortality. Br Med J 1977; 2:1185-1187.

HDL-cholesterol: Just as total cholesterol and triglycerides seemed to be fading, a strong inverse relation between HDL-cholesterol and both coronary and stroke risk has been widely documented. The relation had been identified in 1951 as an explanation for the lower susceptibility of women to coronary disease, the higher HDL then measured as an increased alpha-lipoprotein (Barr *et al*, 1951). But the observation was overlooked in the enthusiasm of relating high cholesterol to CV risk.

In 1975 Miller and Miller published an hypothesis that the rate of progression of atherosclerosis might be an inverse function of the plasma HDL by virtue of a role of the HDL in facilitating the egress of cholesterol out of the artery wall (Miller, 1978). Starting in 1977, a number of studies have documented an inverse relation between HDL and coronary disease (Table 38). The numbered references are provided in Miller's 1978 paper.

One of the better demonstrations is from the Israeli Ischemic Heart Disease Study (Goldbourt and Medalie, 1979). In addition to showing an inverse relation between HDL cholesterol and coronary events, their data show that the risks of smoking and physical inactivity may be related to their effects on HDL levels (Figures 47 & 48).

TABLE 38

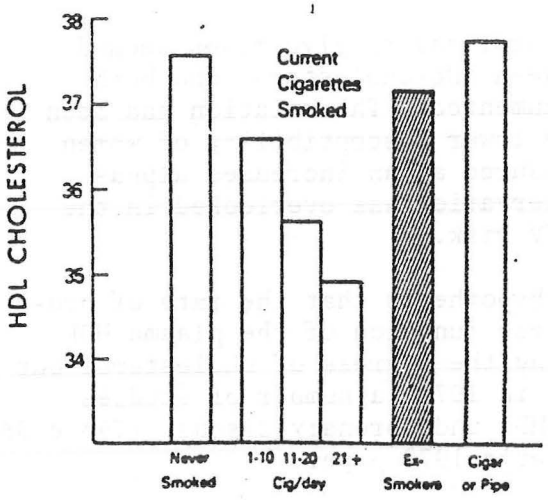
Situations in Which a Low Mean Plasma HDL Cholesterol Concentration is Associated with a High Incidence of Coronary Heart Disease

Coronary risk factors	Disease states	Ethnic group
Hypertriglyceridaemia (17-26)	Diabetes mellitus (22,38-40)	New Zealand Maoris (46)
Obesity (18,20,22,27)	Uraemia (41,42)	
Physical inactivity (25,28-32)	Nephrotic syndrome (43,44)	
Cigarette smoking (32-34)	Chronic cholestasis (44,45)	
Family history of CHD (35,36)		
Male sex (22-24,37)		

Situations in Which a High Mean Plasma HDL Cholesterol Concentration is Associated with a Low Incidence of Coronary Heart Disease

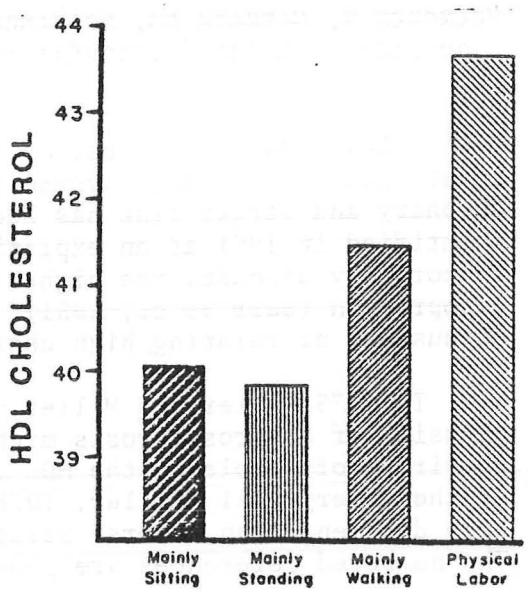
	Ethnic groups
Female sex (22-24,37)	Greenland Eskimos (53)
Athletes (29,30,32)	Black Americans (21,54)
Alcohol consumption (47-49)	Jamaican hill-farmers (25)
Familial hyperalphalipoproteinaemia (50,51)	Turks and Caicos Islanders (49)
Octogenarians (52)	

The HDL levels have been shown to relate to the extent of coronary atherosclerosis by arteriography (Figure 49) (Pearson *et al*, 1979). Moreover, they are strongly related to other known risk factors in normal men (Williams *et al*, 1979) and in children (Berenson *et al*, 1979). Low HDL levels are found in male relatives of patients with coronary disease (Micheli *et al*, 1979) and high HDL levels are found in the kindreds of people who live to be 80 or over (Blueck *et al*, 1977). Some of these long-lived people have familial, primary hyper-alpha-lipoproteinemia--the Methuslasyndrome. The accelerated atherosclerosis seen in patients on chronic hemodialysis may also relate to their low HDL levels and abnormal HDL composition (Rapaport *et al*, 1978).



HDL cholesterol and smoking.

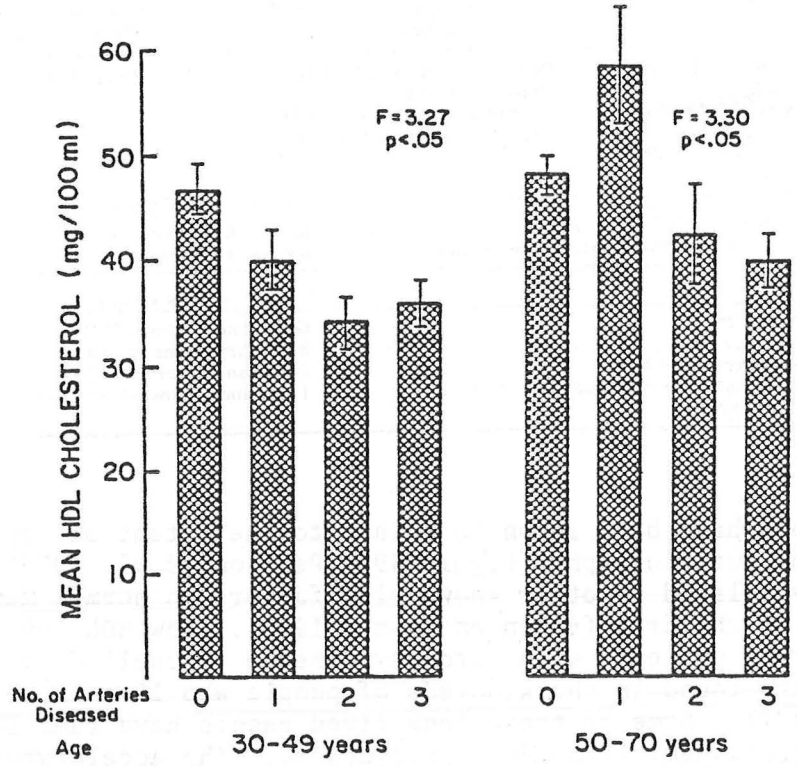
Figure 47



HDL cholesterol and physical activity on the job (1965 data).

Figure 48

Beyong these associations with coronary disease, low HDL levels have also been found in young patients with cerebrovascular disease (Rossner *et al*, 1978).



Mean plasma HDL cholesterol (± 1 standard error of the mean) in white women by age and number of diseased coronary arteries.

Figure 49

How does HDL protect? Miller suggested that HDL might help remove cholesterol out of the artery wall. Subsequent studies have proposed two mechanisms: 1) HDL may facilitate reverse cholesterol transport from cells of the arterial wall back to the liver; 2) HDL may inhibit the uptake of cholesterol by arterial cells by competing with the receptors for the uptake of LDL. The latter mechanism may be involved in the presumed deleterious effects of dietary cholesterol: when healthy people ate 4 to 6 eggs a day for 4 weeks, their HDL changed in its composition and had an increased binding activity to cell-surface receptors of fibroblasts (Mahley *et al*, 1978).

Factors affecting HDL. Two of the situations (exercise and alcohol) listed in Table 38 in which HDL is high in association with a low incidence of coronary heart disease deserve further comment since they can be used to raise HDL. Strenuous running raises HDL (Wood *et al*, 1976). The mechanism may involve an increase in lipoprotein lipase with endurance exercise (Nikkila *et al*, 1978a). The serum of men doing vigorous work contains high levels of HDL and inhibits changes in aortic smooth muscle cells in culture (synthesis of glycosaminoglycans) which are thought to lead to atherosclerosis (Tammi *et al, 1979)*.

As to alcohol, the intake of 5 ounces or more a week clearly raises HDL levels (Castelli *et al*, 1977). It then appears that a useful habit would be to jog to the liquor store at least 3 times a week.

Two drugs raise HDL: estrogens (Krauss *et al*, 1979) and phenytoin (Nikkila *et al*, 1978b). The possible protection of increased HDL with estrogen is presumably overwhelmed by all its adverse effects on blood pressure, clotting, etc. Moreover, the progestin counteracts the HDL-raising effect of estrogen in oral contraceptive pills.

The diet may affect HDL levels. In men given a diet to reduce hyperlipemia (reduced total fat, increased polyunsaturated fatty acids), the HDL averaged 50 mg% compared to 42 mg% in the controls (Hjermann *et al*, 1979). Marked caloric restriction (e.g., 400 calories a day) lowered HDL and raised LDL in 8 normal women (Taskinen and Nikkila, 1979).

REFERENCES:

Berenson GS, Srinivasan SR, Frerichs RR, Webber LS. Serum high density lipoprotein and its relationship to cardiovascular disease risk factor variables in children--the Bogalusa heart study. Lipids 1979; 14:91-98.

Castelli WP, Gordon T, Hjortland et al. Alcohol and blood lipids. The cooperative lipoprotein phenotyping study. Lancet 1977; 2:153-155.

Glueck CJ, Gartside PS, Steiner PM et al. Hyperalpha- and hypbeta-lipoproteinemia in octogenarian kindreds. Atherosclerosis 1977; 27:387-406.

Goldbourt U, Medalie JH. High density lipoprotein cholesterol and incidence of coronary heart disease--the Israeli ischemic heart disease study. Am J Epidemiol 1979; 109:296-308.

Hjermann I, Enger SC, Helgeland A et al. The effect of dietary changes on high density lipoprotein cholesterol: the Oslo study. Am J Med 1979; 66:105-109.

Krauss RM, Lindgren FT, Wingerd J et al. Effects of estrogens and progestins on high density lipoproteins. Lipids 1979; 14:113-118.

Mahley RW, Bersot TP, Innerarity TL et al. Alterations in human high-density lipoproteins, with or without increased plasma-cholesterol induced by diets high in cholesterol. Lancet 1978; 1:807-809.

Micheli H, Pometta D, Jornot C. High density lipoprotein cholesterol in male relatives of patients with coronary heart disease. Atherosclerosis 1979; 32:269-276.

Miller NE. The evidence for the antiatherogenicity of high density lipoprotein in man. Lipids 1978; 13:914-919.

Nikkila EA, Taskinen MR, Rehunen S et al. Lipoprotein lipase activity in adipose tissue and skeletal muscle of runners: relation to serum lipoproteins. Metabolism 1978; 27:1661-1671

Pearson TA, Bulkley BH, Achuff SC et al. The association of low levels of HDL cholesterol and arteriographically defined coronary artery disease. Am J Epidemiol 1979; 109:285-295.

Rapoport J, Aviram M, Chaimovitz C. Defective high-density lipoprotein composition in patients on chronic hemodialysis: a possible mechanism for accelerated atherosclerosis. N Engl J Med 1978; 299:1326-1329.

Rossner S, Mettinger KL, Kjellin KG, Siden A. Normal serum-cholesterol but low HDL-cholesterol concentration in young patients with ischaemic cerebrovascular disease. Lancet 1978; 1:577-579.

Tammi M, Ronnema T, Vihersaari T, Lehtonen A et al. High density lipoproteinemia due to vigorous physical work inhibits the incorporation of {^{3}H}. thymidine and the synthesis of glycosaminoglycans by human aortic smooth muscle cells in culture. Atherosclerosis 1979; 32:23-32.

Taskinen M, Nikkila. Effects of caloric restriction on lipid metabolism in man: changes of tissue lipoprotein lipase activities and of serum lipoproteins. Atherosclerosis 1979; 32:289-299.

Williams P, Robinson D, Bailey A. High-density lipoprotein and coronary risk factors in normal men. Lancet 1979; 1:72-75.

Wood PD, Haskell W, Klein H et al. The distribution of plasma lipoproteins in middle-aged male runners. Metabolism 1976; 25:1249-1257.

THE ROLE OF DIET AND DRUGS

The guidelines presented by Steinberg and Grundy (1978) seem reasonable:

"Dietary advice, aimed at normalizing body weight and reducing plasma lipid levels, should be offered to 1) any individual with a total plasma cholesterol level above 250 mg/dl; 2) any individual with a total plasma triglyceride level above 250 mg/dl; and 3) all patients with clinically evident atherosclerosis, even though their plasma lipid levels are within what we regard as the "normal range."

"All patients with strong family histories (coronary heart disease, stroke, or atherosclerotic peripheral vascular disease), even though their plasma lipid levels are only moderately elevated, should receive dietary advice. Therapeutic goals here should be cholesterol levels less than 225 mg/dl and triglyceride levels less than 200 mg/dl."

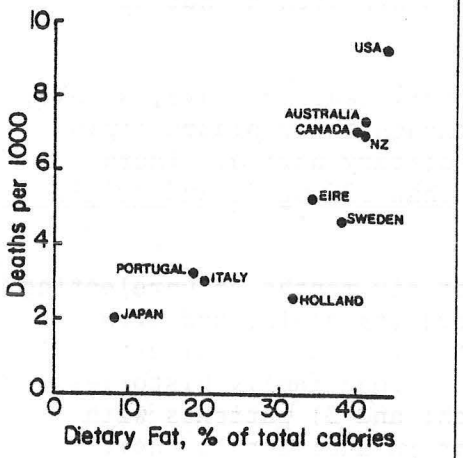
"We consider the use of drugs only after at least six months of unrelenting effort by physician and dietitian has failed to achieve its goals, and even then only in the following groups: 1) patients with clinically manifest atherosclerotic signs and symptoms; 2) patients with strong family histories of atherosclerotic diasease or hyperlipidemia or both; and 3) patients with one or more of the following established risk factors in addition to their hyperlipidemia: hypertension, cigarette smoking, or diabetes mellitus."

After many attempts, there is no firm proof that dietary reductions in total cholesterol have decreased the risks for coronary disease. Even less evidence is available that regression of already formed atherosclerosis is possible. In a few hyperlipoproteinemic patients treated with diet and drugs, regression of femoral atherosclerosis has been observed by angiography (Barndt *et al*, 1977).

Most of the rationale for an altered diet comes from the clear association between the percentage of total calories comprised of fat and CV mortality (Figure 50). The percentage of dietary fat in the U.S. diet has been steadily going up since 1909 (Figure 51), continuing to go up in the last 10 years while CV morality has begun to fall. But this decreased mortality rate may reflect the change in the nature of the fat. Recall Table 4, showing the decrease in saturated fat and the increase in unsaturated fat consumption. Increased dietary polyunsaturated fat almost certainly will lower the blood cholesterol in man (Jackson *et al*, 1978), so the apparent decrease in serum cholesterol levels in the U.S. (Harlan *et al*, 1979) may reflect these dietary changes and may be, as Stamler suggests, part of the reason why CV mortality has fallen.

The need to start early: The dietary changes may need to be started literally from birth in order to be maximally effective. Ten-year-olds in Bogalusa, Louisiana, are eating a heavily "atherogenic" diet and a significant number are obese and hypercholesterolemic (Frank *et al*, 1978). The argument has been made that instead of trying to make specific dietary changes, the simple prevention of obesity during childhood would, in itself, do much to reduce coronary disease (Brook, 1978).

The prudent diet: The type of dietary changes suggested by most is the "Prudent Diet" popularized by the American Heart Association involving a decreased intake of saturated fats, simple sugars, and refined carbohydrate, with polyunsaturated fats comprising less than 25% of total caloric intake (Mann, 1979).



-Fat intake as percent of total calories and circulatory death rates in 1950 in various countries (from Grande').

FIGURE 50

TABLE 39

Revised United States Dietary Goals (1978)

1. **To avoid overweight, consume only as much energy (calories) as is expended; if overweight, decrease energy intake, and increase energy expenditure.**
2. **Increase the consumption of complex carbohydrates and "naturally occurring" sugars from about 28% of energy intake to about 48% of energy intake.**
3. **Reduce the consumption of refined and processed sugars by about 45% to account for about 10% of total energy intake.**
4. **Reduce overall fat consumption from approximately 40% to about 30% of energy intake.**
5. **Reduce saturated fat consumption to account for about 10% of total energy intake; and balance that with poly-unsaturated and mono-unsaturated fats, which should account for about 10% of energy intake each.**
6. **Reduce cholesterol consumption to about 300 mg per day.**
7. **Limit the intake of sodium by reducing the intake of salt to about 5 g per day.**

The question of eggs: How much exogenous dietary cholesterol, particularly in the form of eggs, to allow in the diet is a matter of controversy. Some say keep it below 300 mg a day (Mattson *et al*, 1972); others say 2 eggs a day (about 450 mg of cholesterol) rarely increases the serum cholesterol (Kummerow *et al*, 1977). The egg controversy has been well described in the December, 1978, issue of Nutrition Action, the publication of the Center for Science in the Public Interest.

The entire issue has taken on political overtones with the publication of "Revised U.S. Dietary Goals" in 1978 by the staff of the Senate Select Committee on Nutrition and Human Needs. The recommendations (Table 39)(Figure 52) seem reasonable and in keeping with those made in Scandinavia and England.

Drug therapy: The issue of drug therapy is beyond me. Clofibrate has been found to cause a slight, though statistically insignificant, increase in total deaths, despite a 20% fall in the incidence of CV disease in comparison with control subjects with similar serum cholesterol levels (Report from the Committee, 1978). The bile acid sequestrant, colestipol, may be safer and more effective in lowering cholesterol and reducing CV mortality (Dorr *et al*, 1978; Kuo *et al*, 1979) but may be hard for many to tolerate. A review of drug management has recently been published (Martz, 1979).

As we shall see, aspirin may have a protective effect upon thrombosis and atherosclerosis. It has been shown to inhibit the devlopment of coronary atherosclerosis in monkeys fed an atherogenic diet (Pick *et al*, 1979).

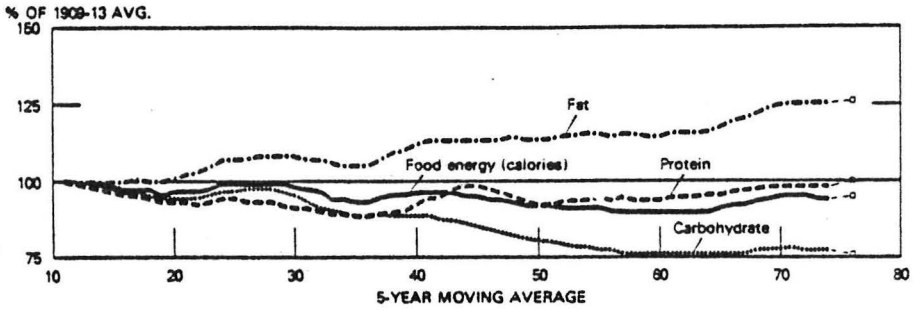


Figure 51

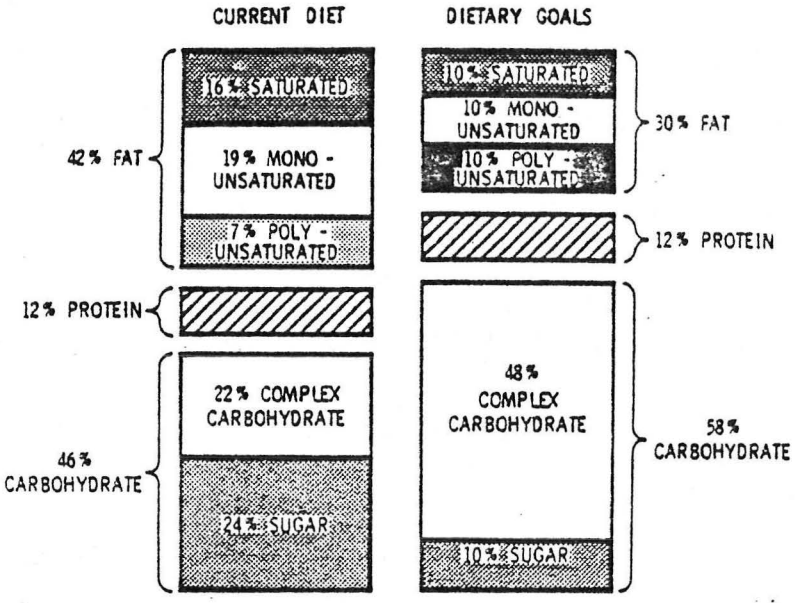


Figure 52

REFERENCES: *The role of diets and drugs*

Barndt R, Blanken horn DH, Crawford DW et al. Regression and progression of early femoral atherosclerosis in treated hyperlipoproteinemic patients. Ann Intern Med 1977; 86:139-146.

Brook CGD. Influence of nutrition in childhood on the origins of coronary heart disease. Postgrad Med 1978; 54:171-174.

Dorr AE, Gundersen K, Schneider JC et al. Colestipol hydrochloride in hypercholesterolemic patients--effect on serum cholesterol and mortality. J Chron Dis 1978; 31:5-14.

Frank GC, Berenson GS, Webber LS. Dietary studies and the relationship of diet to cardiovascular disease risk factor variables in 10-year-old children--the Bogalusa study. Am J Clin Nutri 1978; 31:328-240.

Harlan WR, Oberman A, Carlson S et al. Longitudinal assessment of serum lipoproteins and cholesterol. Clin Res 1979; 221A.

Jackson RL, Taunton OD, Morrisett JD et al. The role of dietary polyunsaturated fat in lowering blood cholesterol in man. Circ Res 1978; 42: 447-453.

Kummerow FA, Kim Y et al. The influence of egg consumption on the serum cholesterol level in human subjects. Am J Clin Nutri 1977; 30:664-473.

Kuo PT, Hayase K, Kostis JB et al. Use of combined diet and colestipol in long-term (7-7½ years) treatment of patients with Type II hyperlipoproteinemia. Circulation 1979; 59:199-211.

Mann JI. Fats and atheroma: a retrial. Br Med J 1979; 1:732-734.

Martz BL. Drug management of hypercholesterolemia. Am Heart J 1979; 97:389-398.

Mattson FH, Erickson A, Kligman AM. Effect of dietary cholesterol on serum cholesterol in man. Am J Clin Nutri 1972; 25:589.

Pick R, Chediak J, Glick G. Aspirin inhibits development of coronary atherosclerosis in cynomolgus monkeys (Macaca Fascicularis) fed an atherogenic diet. J Clin Invest 1979; 63:158-162.

Report from the Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978; 40:1069-1118.

Steinberg D, Grundy SM. Management of Hyperlipidemia. Arch Surg 1978; 113:55-60.

THE MINOR RISK FACTORS

GLUCOSE INTOLERANCE

The Framingham study included the measurement of blood and urine glucose for assessment of risk. The evaluation of glucose tolerance and the recognition of diabetes seem to be rather sloppy, placing all these data in question. Yet, glucose intolerance is used as one of the major criteria for assessing risk. Perhaps the investigators recognized the vagaries of glucose tolerance testing, so they chose not to encase it too rigidly. It seems preferable not to have used it al all.

In Framingham, any one of the following demonstrated glucose intolerance:

1. A diagnosis of diabetes mellitus:
    a. Treatment by a private physician for diabetes
    b. A record of an abnormal 100 g glucose tolerance test--i.e., 160 mg% at 1 hour, 140 at 2 hours, and above basal at 3 hours
    c. On at least 2 exams, a casual blood glucose of 150 mg% or higher
2. Glucosuria, trace or above
3. Casual blood glucose 120 mg% or more

In the first 20 years, 6% of the women and 9% of the men were diagnosed as diabetic. The incidence of CV disease was higher in the diabetics, two-fold for men, 3 times for women (Kannel & McGee, 1979). By statistical manipulations, no indication was noted for any different relationship of risk factors to the subsequent development of CV disease compared to non-diabetics. The data suggest "that the role of diabetes as a CV risk factor does not derive from an altered ability to contend with known risk factors."

Elswhere, diabetes has been found to accelerate coronary atherosclerosis only when its onset is before age 46 years, with little influence by the duration of diabetes (Waller *et al*, 1979). Diabetics may have more hypertension but the relationship is tenuous (Editorial, Lancet, 1978). Certainly hypertensive diabetes should be carefully treated to prevent progressive renal damage (Mogensen, 1976). In Finland, high plasma insulin levels during an oral GTT were found to be associated with an increased incidence of coronary heart disease (Nikkila *et al*, 1979).

In summary, diabetics have more premature cardiovascular disease. The Framingham data are probably too crude to carefully define any more than a loose relationship. Some of the increased risk shown by diabetics may be attributed to their increased prevalence of obesity and hyperlipidemia.

REFERENCES: *Glucose intolerence*

Editorial. Diabetes and hypertension. Lancet 1978; 2:138-139.

Kannel WB, McGee DL. *Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979; 59:8-13.*

Mogensen CE. *Renal function changes in diabetes. Diabetes 1976; 25:872-879.*

Pyorala K, Nikkila EA, Taskinen MR *et al. Plasma insulin as coronary heart disease risk factor. Am J Cardiol 1979; 43:436. (abstract)*

Waller BF, Palumbo PJ, Lie JT, Roberts WC. *Diabeted mellitus, an accelerator or coronary atherosclerosis only when onset is before age 46. A necropsy study of 1172 diabetic coronary arteries and 844 control coronary arteries. Am J Cardiol 1979; 43:436. (abstract)*

OBESITY

By itself, obesity is a weak risk factor for cardiovascular disease. But since it is an important component of other major risk factors--hypercholesterolemia, hypertension, and diabetes--and since it is so easily identified and since it *should* be correctable, attention should be given to its prevention and management.

Degree of risk: Despite a great deal of study, the relationship between obesity and CV risk is not clear. Part of the uncertainty reflects impreciseness in assessing the degree of obesity. Simple weight is inadequate; relative weight is better, weight/height squared (body mass index or BMI), being the preferable measurement; skinfold measurements may be even better.

Beyond problems of measurement, the relationship has been obscured by the interrelationships between obesity and other risk factors. Some are obvious: obesity is more commonly seen in hypertensives. Even here, confounding factors intercede since falsely high blood pressure readings may be recorded in fat people with the use of sphygomomanometers with too short ballons which fail to encircle the arm.

Other associations may not be obvious: smokers tend to be thinner and when they quit smoking gain weight. Nonetheless, despite the possible untoward effects of the weight gain, smokers who quit decrease their morbidity and mortality. Obviously, studies relating obesity and CV risk need to take smoking status into account.

When proper studies and analyses have been done, obesity by itself emerges as only a weak risk factor. In a multinational study of weight and skinfold thickness in over 11,000 men the 5-year incidence of coronary heart disease was not affected by obesity "when the factors of age, blood pressure, serum cholesterol and smoking were comparable" (Keys *et al*, 1972). In the Pooling Project invovling 6 large studies among U.S. men, those aged 40-49 who were in the upper 20% of body weight had a 1.3 greater excess risk (of questionable statistical significance) for major coronary events and there was no excess risk for older men (Pooling Project Research Group, 1978).

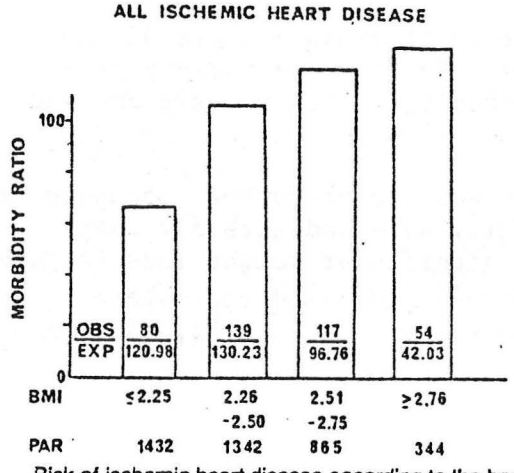
Support for a greater risk for obesity in younger men comes from a 26 year study of 3,983 men in Manitoba (Rabkin *et al*, 1977). Significantly more myocardial infarction, sudden death, and coronary insufficiency were noted in obese men less than 40 years of age after 16 years of follow-up (Figure 53).

As shown in Manitoba, the risk of obesity may take a long time to become obvious. In Framingham, the 18-year risk of cardiovascular disease was clearly increased by a relative weight of 130% or greater (Gordon and Kannel, 1976). Death rates weren't so related but weight loss is so common before death that it would likely obscure any such relationship. Of even greater importance, the Framingham data show a clear increase in coronary risk with weight *gain* (Table 40) (Ashley and Kannel, 1974). Note that men and, to a lesser degree, women who gain 10% or more in relative weight have a significant increase in coronary risk. The weight gain is accompanied by about a 10 mg% increase in serum cholesterol, 5 mm Hg rise in blood pressure, 2 mg% rise in glucose and 0.25 mg% increase in serum uric acid. The investigators conclude "Because it reversibly promotes atherogenic traits like hypertension, diabetes, and hyperlipidemia, reduction of overweight is probably the most important hygienic measure (aside from avoidance of cigarettes) available for the control of cardiovascular disease" (Gordon and Kannel, 1976). From the Framingham data a 20% reduction in the incidence of coronary heart disease might be expected for each 10% reduction in body weight.

Part of the risk from obesity likely arises from its association with increased VLDL and total triglyceride levels and, perhaps most importantly, with decreased HDL levels (Gries *et al*, 1979).

The prevention of obesity: The gross obesity that is more strongly related to CV disease likely is a life-long problem that arises in childhood. Though all fat babies don't become fat adults and all fat adults weren't fat babies, there is a strong correlation between childhood and adult obesity (Charney *et al*, 1976; Hawk and Brook, 1979).

The observation by Hirsch and co-workers that excess feeding during infancy leads to an increase in the number of fat cells and, thereby, a greater propensity to adult obesity has been strongly supported by both cross-sectional and longitudinal studies on 288 subjects ranging in age from 4 months to 19 years (Knittle *et al*, 1979). Obese children have significantly more fat cells after age 1 year than do nonobese children, with another increment during adolescence.



Risk of ischemic heart disease according to the body mass index (BMI [g/cm²]) at entry. EXP = expected; OBS = observed; PAR = population at risk.

← Figure 53

TABLE 40

CORONARY HEART DISEASE RELATIVE ODDS RATIOS CORRESPONDING TO GIVEN CHANGES IN RELATIVE WEIGHT

	Males		Females	
Age:	35–44	45–54	35–44	45–54
Change in relative weight				
−20	0.57	0.62	0.62	0.83
−10	0.76	0.80	0.80	0.94
+10	1.38	1.31	1.31	1.20
+20	1.86	1.68	1.69	1.35

Though other metabolic defects may be involved in obesity (James *et al*, 1978; Schwartz and Brunzell, 1978) along with a reduced amount of physical activity, there is obviously a strong argument to limit infant over-feeding to reduce excessive weight gain and hopefully to thereby prevent adult cardiovascular disease.

The relief of obesity: The need for prevention comes from the inability to get most really fat people to lose weight. This inability reflects numerous difficulties faced by the obese person:

1. Multiple mechanisms are likely involved in potentiating the increased caloric intake and the reduced caloric expenditure responsible for excessive weight gain.

2. Fat people are more neurotic and are under a great deal more socioeconomic pressure (Stunkard, 1975). About 30% of women of low socioeconomic status are obese, whereas fewer than 10% of women of high status are obese.

3. Fat people are disliked and discriminated against by schools, employers, and physicians, adding further to their frustrations (Maimon *et al*, 1979).

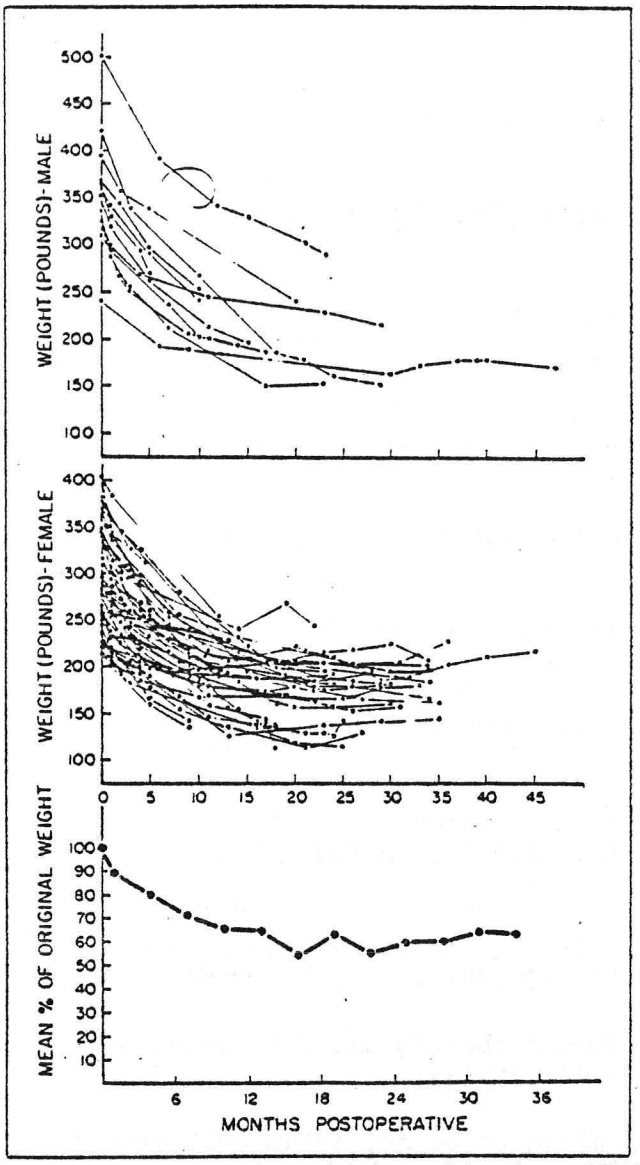
4. When motivated to lose weight, they are confounded by the multiplicity of regimens offered by both legitimate practitioners and fat-quacks (The Diet Jungle, 1975). Much of what is done is of little lasting benefit: of 121 morbidly obese patients who lost significant amounts of weight by prolonged starvation, only 7 maintained their reduced weights over a 7-year follow-up (Johnson and Drenick, 1977).

In the past 10 years, great enthusiasm has arisen for behavior modification which was strongly embraced by Stunkard as showing the "best results ever reported for the outpatient treatment of obesity" (Stundard, 1975). However, only 37 of 144 patients treated by behavioral techniques were able to attain their desired weight and only 9 lost 18 or more kilograms (Currey *et al*, 1977).

The use of behavior modification has been incorporated into the group programs offered by TOPS and Weight Watchers. The latter, now having been used by over 3 million people, is probably the best source of help for the moderately obese individual. For a weekly fee of $4.50 (After a $6 registration charge), the patient will receive an excellent diet and considerable guidance in group "psychotherapy" and behavior modifications.

But nothing usually works for the majority of grossly obese who are at the major risk for cardiovascular disease. For them, a variety of surgical procedures are available and, if the obesity is truly resistant and life-endangering, they should be used.

Surgical treatment: Jejunoileal bypass was the preferred procedure from about 1965-1975. As appraised in 100 carefully screened morbidly obese patients, the procedure usually resulted in significant weight loss (Figure 54) along with reductions in blood pressure, serum lipids, and cholesterol (Halverson *et al*, 1978). But in addition to 5 postoperative deaths, 58% had major



Postoperative weight loss—84 patients, 35/10 cm end-to-end group. Absolute weight loss of males and females and mean per cent of original weight with time.

complications which either required reoperation or were potentially life-threatening. The total listing of side effects is most impressive (Table 41). Liver necrosis and renal damage (Drenick *et al*, 1978) have been particularly bothersome.

For the past few years, gastric bypass has increasingly replaced jejunoileal bypass. Though the operation is more difficult, the postoperative weight loss is comparable and side effects less serious (Griffen *et al*, 1977). In particular, diarrhea is less and liver disease does not appear.

← Figure 54

TABLE 41

Late complications of intestinal bypass

Abnormality	Percent
Abnormal liver function	
Fatty liver by biopsy	84 (64% preop)
Prolonged prothrombin time	52
Hypoalbuminemia	41
Hyperbilirubinemia	24
Increased enzymes	frequent (percent not given)
Liver failure	7
Electrolyte abnormality	
Hypokalemia	65
Hypocalcemia	57
Hypomagnesemia	50
Vitamin deficiencies	
A	82
Folate	81
D	61
B_{12}	20
Cholelithiasis	13
Kidney stones	7
Arthralgias	19
Hyperuricemia	50

REFERENCES: *Obesity*

Ashley FW, Kannel WB. Relation of weight change to changes in atherogenic traits: the Framingham Study. J Chron Dis 1974; 27:103-114.

Charney E, Goodman HC, McBride M et al. Childhood antecedents of adult obesity: do chubby infants become obese adults? N Engl J Med 1976; 295:6-9.

Currey H, Malcolm R, Riddle E. Behavioral treatment of obesity limitations and results with the chronically obese. JAMA 1977; 237:2829-2831.

Berkowitz G, Scheimann E, Neimark P. The Diet Jungle. Consumers Digest, 1975.

Drenick EJ, STanley TM, Border WA et al. Renal damage with intestial bypass. Ann Intern Med 1978; 89:594-599.

Gordon T, Kannel WB. Obesity and cardiovascular disease: the Framingham Study. Clin Eedocrinol Metab 1976; 5:367-375.

Gries FA, Koschinsk T, Berchtold P. Obesity, diabetes, and hyperlipoproteinemia. Atherosclerosis Rev 1979; 4:71-95.

Griffen WO, Young VL, Shevenson CC. A prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity. Ann Surg 1977; 186:500-509.

Halverson JD, Wise L, Wazna MF. Jejunoileal bypass for morbid obesity: a critical appraisal. Am J Med 1978; 64:461-475.

Hawk LJ, Brook CGD. Influence of body fatness in childhood on fatness in adult life. Br Med J 1979; 1:151-152.

James WPT, Bailes J, Davies HL. Elevated metabolic rates in obesity. Lancet 1978; 1:1122-1125.

Johnson , Drenick EJ. Therapeutic fasting in morbid obesity. Arch Intern Med 1977; 137:1381-1382.

Keys A, Aravanis C, Blackburn H, Van Buchem FSP et al. Coronary heart disease: overweight and obesity as risk factors. Ann Intern Med 1972; 77:15-27.

Knittle JL, Timmers K, Ginsberg-Fellner F et al. The growth of adipose tissue in children and adolescents. J Clin Invest 1979; 63:239-246.

Maiman LA, Wang VL, Becker MH et al. Attitudes toward obesity and the obese among professionals. J Am Dietetic Assoc 1979; 74:331-336.

Pooling Project Research Group. Relationship of blood pressure, serum cholestorol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. J Chron Dis 1978; 31:201-306.

Rabkin SW, Mathewson FAL, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba study. Am J Cardiol 1977; 39:452-458.

Schwartz RS, Brunzell JD. Increased adipose-tissue lipoprotein-lipase activity in moderately obese men after weight reduction. Lancet 1978; 2:1230-1231.

Stunkard AJ. Presidential address-1974: from explanation to action in psycosomatic medicine: the case of obesity. Psychosomatic Med 1975; 37:195-236.

SEX AND SEX HORMONES

"Male sex is both the best documented and the least understood of all the risk factors for coronary heart disease" (McGill and Stern, 1979).

Women live on an average of 8 years longer than men. Though women use more medical services and are more frequently diasabled from illness, they have lower death rates and are less frequently afflicted with chronic diseases (Lewis and Lewis, 1977). This almost certainly reflects the protection from atherosclerosis enjoyed by premenopausal women. As women's behavior and roles change, they may come closer to men in mortality: deaths from lung cancer among women now equal those among men.

The Framingham data have been analyzed to see if the sex difference in coronary heart disease can be explained by sex differences in the level of or vulnerability to the known risk factors (cholesterol, blood pressure, cigarette smoking, glucose intolerance, and left ventricular hypertrophy) (Johnson, 1977). In the 45-54 year old group, the difference in CHD risk can be almost entirely explained by the differences in risk factor levels and vulnerability. In the 55-64 and 65-75 year age groups, both of these potential explanations actually favor men, so that other factors must be responsible. Johnson suggests that the continuing sex difference in those over age 55 could be a lasting consequence of the differences in risk factor levels noted in earlier years.

Those women under age 40 who have a cardiovascular event usually have one or more of the known predisposing atherogenic risk factors. In 21 women under 40 with advanced coronary atherosclerosis by angiography, only 3 were free of both hypertension and hypercholesterolemia (Engel *et al*, 1974). Of 24 under age 40 who had a myocardial infarction, one or more major risk factors was usually present (Morris *et al*, 1976). Young women who have premature menopause have an increase in coronary disease which may be in part attributable to their increased frequency of cigarette smoking. Both the chance of premature menopause and the risk for coronary disease accompany smoking.

The use of estrogens: Among young women the use of estrogens is another risk factor. The use of estrogen-containing oral contraceptives increases the risk for myocardial infarction, stroke, and venous thromboembolism (Table 42) (Jick *et al*, 1978). Notice the great additive influence of smoking upon the risk of myocardial infarction. Part of these increased risks likely relate to the known metabolic and hormonal pertubations induced by estrogen: the blood pressure rises, serum lipids increase, clotting is enhanced, glucose tolerance worsens (Kaplan, 1978).

The argument has been made that the increased cardiovascular (and other) risks of pill use are far outweighed by the savings of life and morbidity by the pill's successful prevention of unwanted pregnancy (Putts and Swyer, 1970). With wider access to safe abortion and increasing awareness of the side effects of pill use, the difference beween costs and benefits is less but for most young women who wish to postpone pregnancy, the pill, used under reasonably close supervision, is still the best form of contraception. In view of the large increase in hypertension and myocardial infarction after age 35, women who want no more children should have themselves or their mate sterilized.

TABLE 42

One-Year Risk Estimates for Nonfatal Myocardial Infarction, Stroke, and Venous Thromboembolism in Young Women

Medical Condition	Age, yr	Oral Contraceptive Users, Rate ×1,000*	Oral Contraceptive Nonusers, Rate ×1,000*
Myocardial Infarction			
Royal College of General Practitioners[13]	15 through menopause	0.13(5)	0.02(1)
Boston Collaborative Drug Surveillance Program[1]	27-45†	0.21(20)	0.03(6)
Nonsmokers	27-37	0.02(1)	~0(56,000)‡
	38-45	0.10(1)	~0(62,000)‡
Smokers	27-37	0.12(4)	0.02(1)
	38-45	1.7(14)	0.10(5)
Stroke			
Vessey et al[14]	25-43	0.2(8)	0.08(2)
Royal College of General Practitioners[13]	15 through menopause	0.4(16)	0.10(4)
Venous Thromboembolism			
Boston Collaborative Drug Surveillance Program[3]§	20-44	0.7(31)	0.06(12)
Vessey et al[15]§	16-40	0.3(17)	0.03(20)
Vessey et al[14]§	25-43	0.6(18)	0.08(2)
Royal College of General Practitioners[13]‖	15 through menopause	1.1(41)	0.2(8)

*Numbers in parentheses indicate number of case patients that yielded the estimate.
†There were no cases in this series below 27 years of age.
‡Approximate number of woman years of observation.
§Includes only hospitalized cases.
‖Includes cases of deep-vein thrombosis of the leg diagnosed out of hospital as well as in hospital.

Postmenopausal women who take estrogens have a doubled risk of coronary heart disease (Gordon *et al*, 1978) and about a 3-fold increase in the prevalence of hypertension with doses of Premarin from 0.3 mg/day or more (Pfeffer, 1978).

Postmenopausal changes: Even without estrogens, women have a marked increase in coronary heart disease after the menopause. In Framingham, 2,873 women were followed for 24 years (Gordon *et al*, 1978). No premenopausal women developed a myocardial infarction or died of coronary heart diseases and few had coronary morbidity but such events were common in postmenopausal women (Table 43).

TABLE 43

Coronary Heart Disease Incidence for Women Having a Natural Menopause (Framingham Study: 24-Year Follow-up)

Age and Menopausal Status	Person-Years	Coronary Heart Disease Cases*	
		no.	*/1000/yr*
40 to 44 years old			
Premenopausal	4518	1	0.2
Menopausal	262	0	—
Postmenopausal	280	0	—
45 to 49 years old			
Premenopausal	3266	4 (1)	1.2
Menopausal	1068	1	0.9
Postmenopausal	1752	6 (2)	3.4
50 to 54 years old			
Premenopausal	600	1	1.7
Menopausal	884	6	6.8
Postmenopausal	5704	25 (11)	4.4

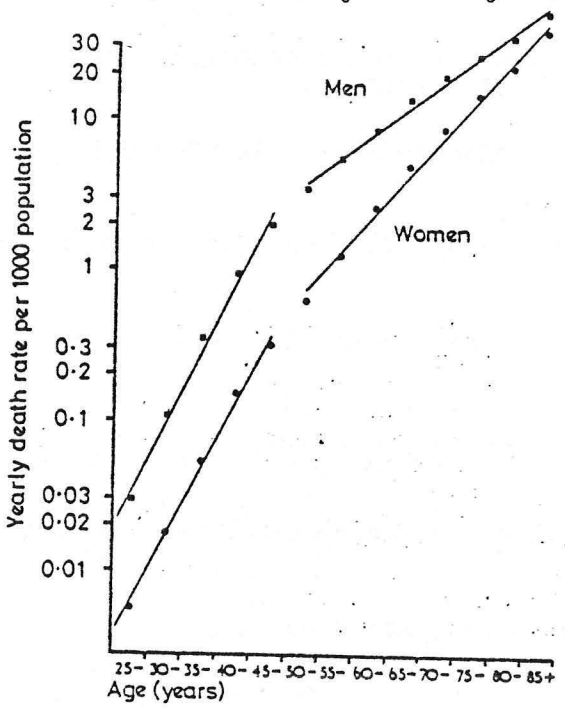
* Parenthetical entries are numbers of coronary heart disease cases presenting as coronary heart disease other than angina pectoris.

The factors responsible for the change in risk after menopause are unknown. One that seems logical is simply the decrease in endogenous estrogen levels. The idea was supported by the finding that serum total and LDL-cholesterol rises at menopause and that these levels were reduced by exogenous estrogen therapy (Russ *et al*, 1955). These findings led to the use of estrogens in several coronary prevention trials. Unfortunately, the results were opposite: more coronary events and deaths were seen in men given estrogen (Coronary Group, 1973).

An interesting idea has been proposed to explain the increase in vascular diseases after menopause: the monthly menses acts to remove atherogenic lipids (Seeley, 1976). The idea could also explain some of the higher incidence of hypertension after menopause since vascular volume would also be reduced by monthly menses. It is true that serum cholesterol and hemoglobin rise after menopause (Hjortland *et al*, 1976). Perhaps the monthly removal of 200-300 ml of blood with its atherogenic and thrombogenic factors could protect the pre-menopause women. People with high hematocrits have more strokes and MI's, probably as a result of the increased viscosity of their blood. Those with lower hematocrits (which would include most menstruating women) may then be protected by their thinner, less viscous blood.

Despite the increased number of events, women appear to keep a relative advantage after menopause but it narrows(Figure 55). In this analysis of mortality data from the entire population of England and Wales, the conclusion was made that women did not in fact lose their protection from coronary heart disease after menopause (Heller and Jacob, 1978). Rather, the data show that after age 50, men seem to lose a factor that had previously put them at increased risk. A logical factor would be androgens.

Men with early coronary disease: Just as women who take estrogens are at additional risk, young men who have a myocardial infarction tend to have higher *endogenous* estrogen levels but normal testosterone and androstenedione levels (Figure 56) (Entrican *et al*, 1978).



-Death rates from ischaemic heart disease in men and women according to age (England and Wales 1970-4).

Figure 55

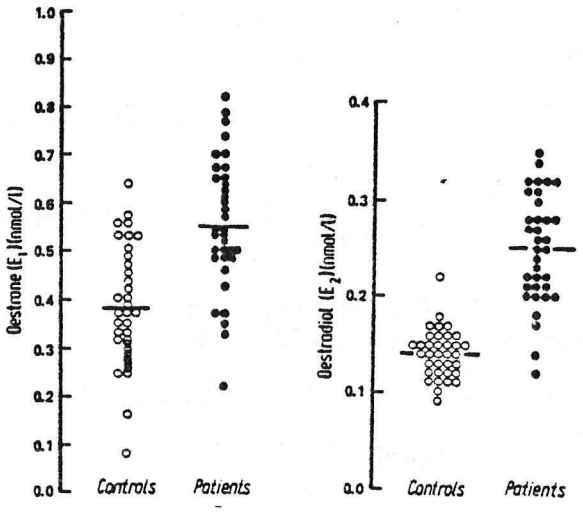


Figure 56

Estrogen therapy of type II hyperlipoproteinemia: The situation gets more complicated: though exogenous estrogen doesn't protect men from coronary disease, it may protect postmenopausal women who are at increased risk from raised serum total and LDL-cholesterol (type II). When oral estradiol-17β-valerianate, 2 mg daily, was given to 17 postmenopausal women, their serum total and LDL decreased by 18% and serum HDL increased by 30% (Tikkanen *et al*, 1978).

REFERENCES: *Sex and Sex hormones*

Coronary Drug Project Research Group. Findings leading to discontinuation of the 2.5 mg/day estrogen group. JAMA 1973; 226:652-657.

Engel HJ, Page HL, Campbell B. Coronary artery disease in young women. JAMA 1974; 230:1531-1534.

Entrican JH, Beach C, Carroll D et al. Raised plasma oestradiol and oestrone levels in young survivors of myocardial infarction. Lancet 1978; 2:487-489.

Gordon T, Kannel WB, Hjortland MC et al. Menopause and coronary heart disease. The Framingham study. Ann Intern Med 1978; 89:157-161.

Heller RF, Jacobs HS. Coronary heart disease in relation to age, sex, and the menopause. Br Med J 1978; 1:472-474.

Hjortland MC, McNamara PM, Kannel WB. Some atherogenic concomitants of menopause: the Framingham study. Am J Epidemiol 1976; 103:304-311.

Jick H, Dinan B, Herman R et al. Myocardial infarction and other vascular diseases in young women. JAMA 1978; 240:2548-2552.

Johnson A. Sex differentials in coronary heart disease: the explanatory role of primary risk factors. J Health Social Behav 1977; 18:46-54.

Kaplan NM. Cardiovascular complications or oral contraceptives. Ann Rev Med 1978; 29:31-40.

Lewis CE, Lewis MA. The potential impact of sexual equality on health. N Engl J Med 1977; 297:863-869,

McGill HC, Stern MP. Sex and atherosclerosis. Atherosclerosis Rev 1979; 4:157-242.

Morris DC, Hlrst JW, Logue RB. Myocardial infarction in young women. Am J Cardiol 1976; 38:299-304.

Pfeffer RI. Estrogen use, hypertension and stroke in postmenopausal women. J Chron Dis 1978; 31:389-398.

Potts DM, Swyer GIM. Effectiveness and risks of birth-control methods. Br Med Bull 1970; 26:26-30.

Russ EM, Eder HA, Barr DP. Influence of gonadal hormones on protein-lipid relationships in human plasma. Am J Med 1955; 19:4-24.

Seely S. Possible reasons for the comparatively high resistance of women to heart disease. Am Heart J 1976; 91:275-280.

Tikkanen MJ, Nikkila EA. Natural oestrogen as an effective treatment for type II hyperlipoproteniaemia in postmenopausal women. Lancet 1978; 2:490-491.

BEHAVIOR AND STRESS

A relationship between premature coronary disease and behavior has long been recognized. Osler noted that young patients with coronary disease were typically "a keen and ambitious man, the indicator of whose engine is always set a full speed ahead" (Osler, 1896).

But is was Meyer Friedman and Ray Rosenman in the late 1950's who formulated the concept that behavior patterns could be divided into two types, A and B, and that these were related to the incidence of coronary heart disease. The scientific cornerstone of their concept is the Western Collaborative Group Study in which 3,145 men aged 39 to 59 were characterized and prospectively followed for 8.5 years. The type A subjects had 2.37 times the incidence of new coronary heart disease (Rosenman *et al*, 1976).

The type A individual has been characterized as having these traits:

--Intense striving for achievement

--Competitiveness

--Being easily provoked

--Impatience

--Time urgency; preoccupation with deadlines

--Abruptness of gestures and speech

--Overcommitment to vocation or profession

--Excesses of drive and hostility

Since the characterization of types A and B had no formal, structured basis, the Jenkins Activity Survey (JAS) was established as an objective instrument for making the distinction using a self-administered, 61 term, computer-graded questionnaire. It too was found to be significantly associated with CHD incidence (Jenkins *et al*, 1974). Subsequently, different patterns of response to the JAS have been observed between those type A's who subsequently develop angina from those who subsequently have an MI (Jenkins *et al*, 1978).

Various physiological differences between A and B in their responses to various stresses have been sought to explain their different propensities to CHD. Among those which have been found are:

--Greater variability in serum cholesterol (Friedman and Rosenman, 1959)

--Greater rises in diastolic blood pressure during cold-pressor stress (Keys *et al*, 1971).

--A greater rise in plasma norepinephrine during competition (Friedman *et al*, 1975)

--Larger digital vasomotor responses to testing (Van Egeren, 1979)

More and more, behavioral scientists and cardiologists seem to be grudgingly accepting the validity of type A behavior as being a risk for CHD, independent of other known risks. A useful summary of current opinion and data is a book CORONARY-PRONE BEHAVIOR, ed. by TM Dembrowski *et al*, Springer-Verlag, New York, 1978.

However, not all find that type A behavior relates to CHD risk (Haynes *et al*, 1978). Moreover, other psychosocial contributions to CHD risk are not included in the present category of type A behavior. The major problem is the virtual absence of any evidence that type A behavior can be changed and, if it could, that the risk of CHD would thereby be reduced.

In their book, Friedman and Rosenman make these suggestions for "drills" to change type A behavior:

1. Positive reinforcement of non-Type A behavior; for example, scheduling non-business lunch hours, which can be highly reinforcing if taken in settings that offer cues for non-Type A behavior, such as walks in the park and browsing through bookstores.

2. Avoidance responding, described as avoiding situations and interactions that elicit feelings of time pressure, hostility, etc. (Examples include not wearing a watch, not making a "things to do today" list, and not scheduling back-to-back activities throughout the work day).

3. Other self-control techniques.

Hopefully, the current interest in behavioral aspects of cardiovascular disease will provide objective data concerning the value of such behavior modification.

Considerable evidence supports a special role of psychological stress by hypertension, which may obviously be responsible for some of the risk for CHD (Kaplan, 1978).

Other psychosocial relations: Among 6,928 adults in Alameda County, California, those who lack social and community ties were more likely to die during a 9-year study (Berkman and Syme, 1979). The relative risks for the most isolated compared to those with the most social contact were 2.3 for

men and 2.8 for women. The association was independent of various other known risk factors, use of health services and socioeconomic status.

Mortality from coronary disease, at least in England, is becoming more and more prevalent among the poor, while its frequency is changing little if at all among the upper socioeconomic groups (Marmot *et al*, 1978). This change can be related to relatively more cigarette smoking, more sugar consumption, and less consumption of wholemeal bread but not to differences in fat intake. Similarly, people with less education have a greater likelihood of sudden coronary death (Jenkins, 1978) as well as a higher frequency of hypertension (Dyer *et al*, 1976). These relationships are not explained by other known risk factors.

REFERENCES: *Behavior and stress*

Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda Coutny residents. Am J Epidemiol 1979; 102:186-204.

Dyer AR, Stamler J, Shekelle RB et al. The relationship of education to blood pressure findings on 40,000 employed Chigoans. Circulation 1976; 987-992.

Friedman M, Byers SO, Diamant J. Plasma catecholamine response of coronary-prone subjects (type A) to a specific challenge. Metabolism 1975; 24:205-210.

Haynes SG, Levine S, Scotch N et al. The relationship of psychosocial factors to coronary heart disease in the Framingham study. Am J Epidemiol 1978; 107:362.

Jenkins CD. Low education: a risk factor for death. N Engl J Med 1978; 299:95-96.

Jenkins CD, Rosenman RH, Zyzanski SJ. Prediciton of clinical coronary heart disease by a test for the coronary-prone behavior pattern. N Engl J Med 1974; 290:1271-1275.

Jenkins CD, Zyzanski SJ, Rosenman RH. Coronary-prone behavior: one pattern or several. Psychosom Med 1978; 40:25-43.

Kaplan NM. Stress, the sympathetic nervous system and hypertension. J Human Stress 1978; 4:29-34.

Keys A, Tyalor HL, Blackburn H et al. Mortality and coronary heart disease among men studied for 23 years. Arch Intern Med 1971; 128:201-214.

Marmot MG, Adelstein AM, Robinson N. Changing social-class distribution of heart disease. Br Med J 1978; 2:1109-1112.

Osler W. Lectures on angina pectoris and allied states. New York Med J 1896; 177-183.

Van Egeren LF. Social interactions, communications, and the coronary-prone behavior pattern: a psychophysiological study. Psychosom Med 1979; 41: 2-18.

FAMILY HISTORY

A family history of premature cardiovascular disease is usually listed as a risk factor. Little published data are available to document the vaolidity of this inclusion. Most of the risk may be attributable to the known familial tendency for hypertension, obesity, and certain forms of hypercholesterolemia.

According to some analyses, longevity itself is little, if at all, correlated between parents and children or between siblings (Philippe, 1978). The similarities in life span within families is largely attributable to common environment and way of life.

Whatever the reasons, the offspring of short-lived parents have a considerably higher death rate from coronary, cerebrovascular, and hypertensive diseases (Hammond *et al*, 1971). Among middle-aged Swedish men, the parents and siblings of those with few risk factors for CV disease had only about half as many CV diseases as did the parents and siblings of those with many risk factors (Hedstrand and Aberg, 1978). Among Finnish men who developed angina before age 56, there was five times more coronary artery disease in fathers and brothers and 2.5 times more in sisters than among the family members of controls fromthe same area (Rissanen and Nikkila, 1977). The patients' siblings who were free of clinical coronary disease had 2 to 6 times more hypertension, hyperlipemia, and diabetes than did the controls' siblings. So, whether because of shared genes or, more likely, shared environments and health habits, families do tend to show a general pattern of CV risk. But the family history should probably not be given a major place in the determination of relative risk.

REFERENCES: *Family history*

Hammond EC, Garfinkel L, Seidman H. Longevity of parents and grand-parents in relation to coronary heart disease and associated variables. Circulation 1971; 43:31-44.

Hedstrand H, Aberg H. Familial history in males at low and high risk for cardiovascular disease. Prev Med 1978; 7:15-21.

Philippe P. Familial correlations of longevity: an isolate-based study. Am J Med Genetics 1978; 2:121-129.

Rissanen AM, Nikkila EA. Coronary artery disease and its risk factors in families of young men with angina pectoris and in controls. Br Heart J 1977; 39:875-883.

ALCOHOL

Moderate drinkers (i.e. 1 to 3 drinks per day) have less coronary heart disease and this may be related to their higher HDL-cholesterol levels (Yano *et al*, 1977; Castelli *et al*, 1977). A rather striking inverse relation between per capita beer consumption and coronary mortality has been noted in data from 20 countries (La Porte *et al*, 1979) (Figure 57).

On the other hand, the blood pressures of those who drink 3 or more drinks a day are higher, with a higher prevalence of hypertension (Klatsky *et al*, 1977). Those who consume more than 5 drinks a day die sooner from both cardiovascular and other causes (Dyer *et al*, 1977).

Some of the hyperuricemia seen in untreated hypertensives may be related to their alcohol intake (Ramsay, 1979). The author considers a uric acid level above 8.4 mg% as being highly suggestive of heavy alcohol consumption. Similarly, drinking hypertensives may present with significant liver dysfunction (Ramsay, 1977).

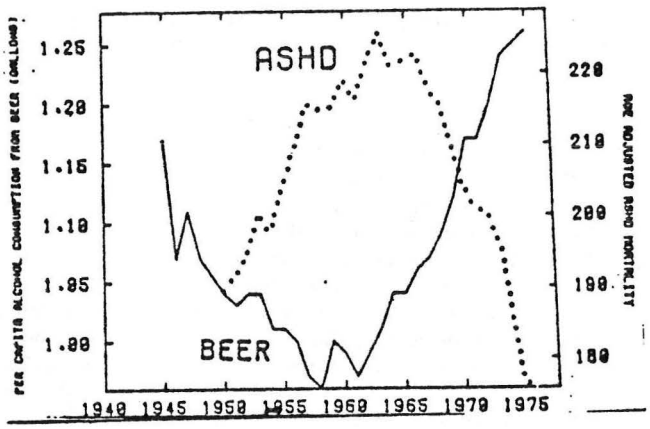


Figure 57

REFERENCES: Alcohol

Castelli WP, Doyle JT, Gordon T et al. Alcohol and blood lipids. The cooperative lipoprotein phenotyping study. Lance 1977; 2:153-155.

Dyer AR, Stamler J, Oglesby P et al. Alcohol consumption, cardiovascular risk factors, and mortality in two Chicago epidemiologic studies. Circulation 1977; 56:1067-1074.

Klatsky AL, Friedman GD, Siegelaub AB. Alcohol consumption and blood pressure. N Engl J Med 1977; 296:1194-1200.

LaPorte RE, Kuller LH, Cresanta JL. Geographic and secular relationship of alcohol intake to ASHD death rates. Abstract Conference on CVD Epidemiology, New Orleans, 1979; #17:43.

Ramsay LE. Liver dysfunction in hypertension. Lancet 1977; 2:111-114

Ramsay LE. Hyperuricaemia in hypertension: role of alcohol. Br Med J 1979; UL653-654.

Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. N Engl J Med 1977; 297:405-409.

PHYSICAL ACTIVITY

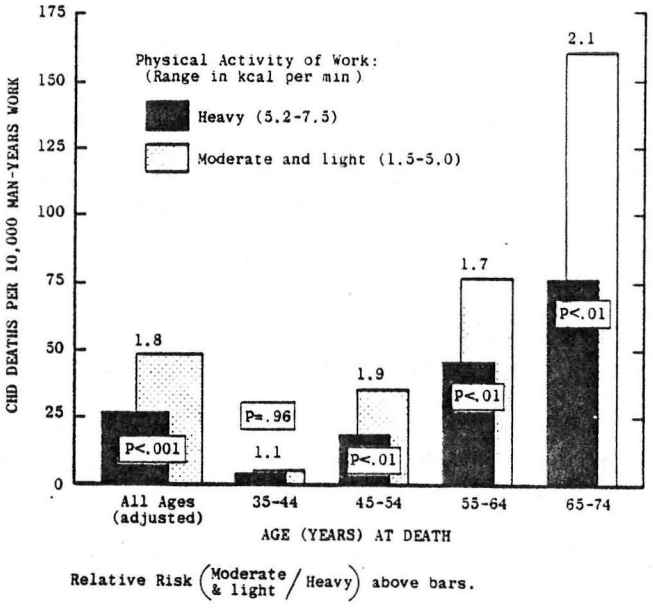
Increased physical acitivty during work (Paffenbarger *et al*, 1978) or leisure time (Morris *et al*, 1973) is associated with a reduced death rate from coronary heart disease. The evidence for an increased risk for CHD with inactivty and a decreased risk with increased activity is overwhelming (Table 43). This table is taken from Fletcher and Cantwell's book, Exercise and Coronary Heart Diseasem, C.C. Thomas, Springfield, 1979.

TABLE 43

EPIDEMIOLOGY STUDIES: PHYSICAL ACTIVITY AND CORONARY HEART DISEASE (CHD)

Type of Study	Major Author	Population Size	Occupation	Correlations of Physical Inactivity to CHD
Retrospective				
London Transport	Morris	31,000	Drivers vs. conductors	Yes
North Dakota	Zukel	20,000	Farmers vs. others	Yes
U.S. Railroad	Taylor	100,000	Switchmen vs. clerks	Yes
Evans Co.	Hames	5,000	Laborers vs. white collar	Yes
HIP of New York	Frank	301	Less active, intermediate, more active	Yes
Peoples Gas Co.	Stamler	1,500	Blue collar vs. white collar	Yes
College Oarsmen	Prout	172	Athletes vs. nonathletes	No (but athletes lived longer)
Danish athletes	Schnohr	307	Athletes vs. nonathletes	No (but athletes lived longer)
Harvard football	Pomeroy		Athletes vs. nonathletes	No CHD in athletes who kept active after graduation
Harvard athletes	Polednak	681	Athletes (1 or 2 letter) vs. Athletes (3 letters or more)	More CHD in lettermen with three letters or more
Prospective				
San Francisco	Paffenbarger	3,300	Cargo workers vs. clerks	Yes
Framingham	Kannel	5,000	Active vs. sedentary	Yes
Seven Countries	Keys	12,000	Active vs. sedentary	No
Goteborg	Werko	834	Active vs. sedentary	Yes
British Civil Servants	Morris	16,882	Active vs. inactive (leisure time)	Yes
Pathology				
England	Morris	3,800	Light, moderate, heavy	Yes
DeMar	White	1	Marathon runner	Enlarged diameter of coronary arteries
Rehabilitation				
Israel	Gottheiner	1,103	Coronary patients	Positive trend
Case Western Reserve	Hellerstein	100	Coronary patients	Positive trend
Canada	Rechnitzer	68	Coronary patients	Positive trend

The degree of risk is shown nicely in Paffenbarger's 22-year study of 3,686 San Francisco longshoremen (Figure 58). Those whose work is judged as "heavy" have about one-half the CHD morality as those whose work is "moderate and light." Here again, this association is independent of other known risk factors.



Death Rates from Coronary Heart Disease (CHD), 1951-1972, According to Physical Activity of Work and Age at Death.

Figure 58

Those who work or play vigorously may have many reasons for better cardiovascular health, including lower body weight, lower blood pressure, lower serum cholesterol, and less smoking (Cooper *et al*, 1976). Heavy exercise will raise plasma HDL-cholesterol while it lowers triglycerides (Lehtonen and Viikari, 1978). However, if body weight is kept constant during exercise by extra eating, HDL did not rise and, in some, may fall (Lipson *et al*, 1979).

Unfortunately, exercise in presumably normal people may bring out ventricular ectopic beats (Ekblom *et al*, 1979) but their frequency will usually diminish with physical conditioning (Blackburn *et al*, 1973). Moreover, even heavy, life-long exercise (e.g., cross-country skiing) will not halt the age-dependent decline in physical performances or the appearance of electrocardiogrphic evidences of coronary disease (Lie and Erikssen, 1978).

Even marathon runners may die from coronary disease (Green *et al*, 1976), but their likelihood is markedly reduced from less fit people (Editorial, Lancet, 1978). Interestingly, marathon runners have a much lower family history of coronary disease (Siegel *et al*, 1979).

Isometric exercise offers no advantages and may be harmful to people with high blood pressure. Shoveling snow, involving considerable isometric activity, increases the death rate from ischemic heart disease (Glass and Zack, 1979). A much more enjoyable form of isometric exercise, sexual intercourse, will also cause the pulse and blood pressure to rise in presumably normal men (Nemec *et al*, 1976).

REFERENCES: *Physical activity*

Blackburn H, Taylor HL, Hamrell B et al. Premature ventricular complexes induced by stress testing: their frequency and response to physical conditioning. Am J Cardiol 1973; 31:441-449.

Cooper KH, Pollock ML, Martin RP et al. Physical fitness levels vs selected coronary risk factors: a cross-sectional study. JAMA 1976; 236:166-169.

Editorial. Marathon runners and ischaemic heart disease. Lancet 1978; 2:718-719.

Ekblom B, Hartley LH, Day WC. Occurrence and reproducibility of exercise-induced ventricular ectopy in normal subjects. Am J Cardiol 1979; 43:35-46l

Glass RI, Zack MM. Increase in deaths from ischaemic heart disease after blizzards. Lancet 1979; 1:485-487.

Green LH, Cohen SI, Kurland G. Fatal myocardial infarction in marathon racing. Ann Intern Med 1976; 84:704-706.

Lehtonen A, Viikari J. Serum triglycerides and cholesterol and serum high-density lipoprotein cholesterol in highly physically active men. Acta Med Scand 1978; 204:111-114.

Lie H, Erikssen J. ECG aberrations, latent coronary heart disease and cardiopulmonary fitness in various age groups in Norwegian cross-country skiers. Acta Med Scand 1978; 203:503-507.

Lipson LC, Bonow RI et al. Effects of exercise on human plasma lipoproteins. Am J Cardiol 1979; 43:409. (abstract)

Morris JN, Adam C, Chave SPW et al. Vigorous exercise in leisure-time and the incidence of coronary heart-disease. Lancet 1973; 1:333-339.

Nemec ED, Mansfield L, Kennedy JW. Heart rate and blood pressure responses during sexual activity in normal males. Am Heart J 1976; 92:274-277.

Paffenbarger RS, Hale WE. Work activity and coronary heart mortality. N Engl J Med 1975; 292:545-550.

Paffenbarger RS, Brand RJ, Sholtz RI, Jung DL. Energy expenditure, cigarette smoking, and blood pressure level as related to death from specific diseases. Am J Epidemiol 1978; 108:12-18.

Siegel AJ, Hennekens CH, Rosner B, Karlson LK. Paternal history of coronary heart disease among marathon runners. AFCR Clinical Epidemiol 1979; 27:223A.

COFFEE

In 1973 the Boston Collaborative Drug Surveillance Program reported a positive association between coffee consumption and acute MI, a 60% increase in risk for 1 to 5 cups per day, a 120% increase for 6 or more (Jick *et al*, 1973). Since then three other large studies have failed to confirm this association (Dawber *et al*, 1974; Wilhelmsen *et al*, 1977; Heyden *et al*, 1978). An association between coffee drinking and smoking is common.

Wilhelmsen *et al* found no association between coffee and coronary disease in a prospective study but did associate increased coffee drinking with MI retrospectively suggesting that people may drink more coffee with increased stress before an MI (Wilhelmsen *et al*, 1977).

The caffeine equivalent to 2-3 cups of coffee, when taken orally by young non-coffee drinkers, increased plasma renin activity (57%), plasma norepinephrine (75%), and plasma epinephrine (201%) (Robertson *et al*, 1978). Thus, in the non-habituated, a load of caffeine will set off the sympathetic nervous system. The applicability of this study to ordinary coffee drinking is unknown.

REFERENCES: Coffee

Dawber TR, Kannel WB, Gordon T. Coffee and cardiovascular disease: observations from the Framingham study. N Engl J Med 1974; 291:871-874.

Heyden S, Tyroler HA, Heiss G, Hames CG et al. Coffee consumption and mortality: total mortality, stroke mortality, and coronary heart disease mortality. Arch Intern Med 1978; 138:1472-1475.

Jick H, Miettinen OS, Neff RK et al. Coffee and nyocardial infarction. N Engl J Med 1973; 289:63-67.

Robertson D, Frolich JC, Carr K et al. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med 1978; 298:181-186.

Wilhelmsen L, Tibblin G, Elmfeldt D et al. Coffee consumption and coronary heart disease in middle-aged Swedish men. Acta Med Scand 1977; 201:547-552.

HYPERURICEMIA

The data are soft but it appears that, by itself, hyperuricemia is only a weak risk factor for CV morbidity (Steele, 1979). Most of its risk seems related to its association with obesity, diabetes, hypertension, and heavy alcohol consumption.

REFERENCES: Hyperuricemia

Steele TH. Asymptomatic hyperuricemia: pathogenic or innocent bystander? Arch Intern Med 1979; 139:24-25.

INCREASED HEMATOCRIT

In Framingham, otherwise healthy men and women with hemoglobin levels in the high normal range (exceeding 15 and 14 g, respectively) had double the chance of developing a stroke (Kannel *et al*, 1972). In patients with blood dyscrasias, having an increased hematocrit and whole blood viscosity, cerebral blood flow was reduced (41.4 ml/100 g/min with hematocrit of 49%); after phlebotomy, the hematocrit fell to 42.6% and cerebral blood flow increased to 62.1 ml/100 g/min (Thomas, 1979).

REFERENCES: *Increased hematocrit*

Kannel WB, Gordon T, Wolf PA. Hemoglobin and the risk of cerebral infarction: the Framingham study. Stroke 1972; 3:409-420.

Thomas DJ et al. Summary of Ninth International Salzburg Conference on Cerebrovascular Disease. Stroke 1979; 10:113-116.

ASPIRIN DEFICIENCY

The title is obviously facetious. However aspirin may prevent stroke and coronary disease by inhibiting platelet aggregation. Platelet aggregation is likely involved in the formation of atheromatous plaques and may also be involved in thrombosis--both pathogenetic mechanisms for coronary and cerebral vascular disease. So the intake of aspirin may be looked upon as a way to slow down the underlying processes of atherothrombotic disease, not by replacing a deficiency but by preventing a pathologic process.

How does aspirin work?

Aspirin prevents platelet aggregation by affecting prostaglandin biosynthesis. It does so by inhibiting the action of the cyclooxygenases which are needed for the conversion of arachidonic acid to prostaglandin G_2 (Figure 59). This enzyme inhibition occurs wherever prostaglandins are synthesized but the degree and duration vary in different sites.

Two types of prostaglandins are involved in platelet aggregation. Within platelets, the primary prostaglandin formed is Thromboxane A_2, which has a pro-aggregating effect. Within the endothelial cells lining blood vessels, another prostaglandin, prostacyclin, is formed which has a powerful anti-aggregating effect.

Aspirin inhibits the cyclooxygenase in both places but the endothelial cells are inhibited only as long as the aspirin is present and recover fully by 36 hours (Jaffe and Weksler, 1979). Moreover, only small amounts of prostacyclin inhibits platelet aggregation, so the protective action should be returned within a few hours after aspirin is withdrawn.

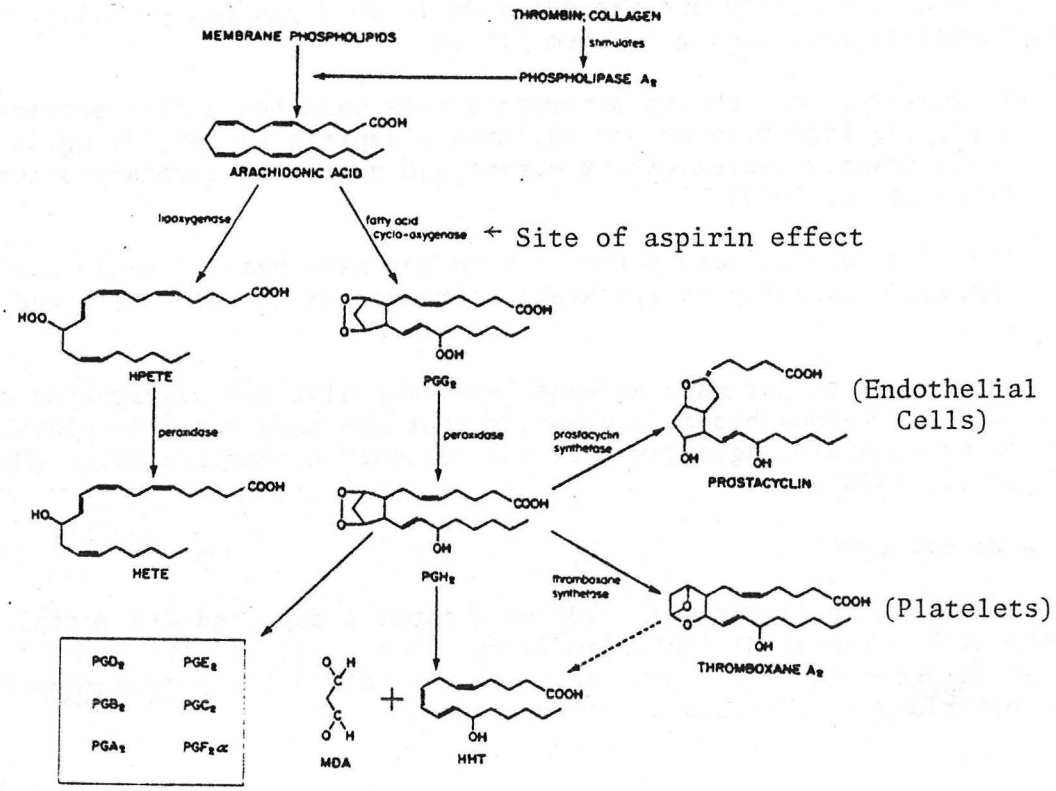


Figure 59

On the other hand, within platelets, aspirin causes irreversible acetylation of cyclooxygenase, so that once exposed to aspirin, that generation of platelets cannot make thromboxane A_2. Only with a new generation of platelets (which have a 4 day half-life) will thromboxane A_2 return and this becomes measurable 48 hours after aspirin exposure.

Thus during most of the first 48 hours after aspirin intake, endothelial cells can produce enough prostacyclin to offer anti-aggregating protection whereas platelets are not able to make thromboxane A_2 with its pro-aggregating potential.

These clinical points follow: 1) only a small dose of aspirin is needed to inhibit cyclooxygenase, 600 mg orally being adequate; 2) aspirin should only be taken once daily and perhaps no more than every 2 to 3 days to maintain the desired inhibition of platelet thromboxane A_2 but allow the formation of prostacyclin.

Does aspirin prevent vascular disease?

Probably, but the evidence remains incomplete. As for coronary disease, two clinical studies support protection by aspirin in prevention of recurrences of myocardial infarction (Boston Group, 1974; Elwood *et al*, 1974) and one denies any protection (Hennekens *et al*, 1978). As for cerebrovascular disease, one study found limited success (Fields *et al*, 1977), another a very significant, 48% reduction of risk in men but no effect in women (Canadian Group, 1978). Both studies involved patients with transient ischemic attacks (TIA) who would be likely to proceed soon to stroke.

Is it likely that aspirin can offer primary protection?

Here again, probably but the evidence is only now being collected. There are experimental data making it seem likely:

--In monkeys, who develop atherosclerosis when fed a high butter-cholesterol diet, the ingestion of one children's aspirin tablet (81 mg) a day significantly decreased the extent and number of coronary atheroma (Pick *et al*, 1979).

--The platelets of some patients with coronary heart disease have an increased capacity to synthesize thromboxane A_2 (Szezeklik and Gryglewski, 1978)

--Patients with coronary disease have less platelet aggregation in their coronary venous blood, suggesting that the more reactive platelets formed platelet aggregates in the coronary microcirculation (Mehta *et al*, 1979).

What else may work?

Sulfinpyrazole (Anturane), 200 mg 4 times a day, reduced mortality in patients with a recent MI (Anturane Group, 1978). It did not work in the Canadian stroke study. The drug seems to work differently from aspirin to inhibit platelet adhesion and aggregation.

Dipyridamole (Persantin) acts to inhibit platelet aggregation by inhibiting the enzyme phosphodiesterase in the platelets. Its action depends on the stimulation of platelet cyclic AMP by circulating prostacyclin (Moncada and Korbut, 1978). Therefore, it will not work in the presence of multiple high doses of aspirin which completely inhibit prostacyclin synthesis but it will work with low doses of aspirin, which only diminish synthesis.

Propranolol exerts some anti-aggregating effect which seems additive to aspirin's (Keber *et al*, 1979).

Lesser amounts of saturated fat in the diet may decrease platelet aggregation (Renaud *et al*, 1978). On the other hand, a fatty acid which is present in the Eskimo diet, eicosapentaenoic acid, leads to the formation of a different thromboxane (A_3) which does not aggregate platelets while at the same time is utilized to make a prostacyclin that has anti-aggregating effects (Dyerberg *et al* 1978). This has been invoked to explain the low incidence of myocardial infarctions among Eskimos.

REFERENCES: *Aspirin deficiency*

Anturane Reinfarction Trial Research Group. Sulfinpyrazone in the prevention of cardiac death after myocardial infarction. N Engl J Med 1978; 298: 289-295.

Boston Collaborative Drug Surveillance Group. Regular aspirin intake and acute myocardial infarction. Br Med J 1974; 1:440-443.

The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978; 299:53-59.

Dyerberg J, Bang HO, Stoffersen E. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978; 2:117-119.

Elwood PC, Cochrane AL, Burr ML. A randomized controlled trial of acetylsalicylic acid in the secondary prevention of mortality from myocardial infarction. Br Med J 1974; 1:436-440.

Fields WS, Lemak NA, Frankowski RF. Controlled trial of aspirin in cerebral ischemia. Stroke 1977; 8:301.

Hennekens CH, Karlson LK, Rosner B. A case-control study of regular aspirin use and coronary deaths. Circulation 1978; 58:35-38.

Jaffe EA, Weksler BB. Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. J Clin Invest 1979; 63:532-535.

Keber I, Jerse M, Keber D et al. The influence of combined treatment with propranolol and acetylsalicylic acid on platelet aggregation in coronary heart disease. Br J Clin Pharm 1979; 7:287-291.

Mehta P, Mehta J, Pepine CJ et al. Platelet aggregation across the myocardial vascular bed in man: I. Normal versus diseased coronary arteries. Thrombosis Res 1979; 14:423-432.

Moncada S, Korbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1978; 1:1286-1289.

Pick R, Chediak J, Glick G. Aspirin inhibits development of coronary atherosclerosis in Cynomolgus monkeys (Macaca Fascicularis) fed an atherogenic diet. J Clin Invest 1979; 63:158-162.

Renaud S, Dumont E, Godsey F et al. Platelet functions in relation to dietary fats in farmers from two regions of France. Thrombos. Haemostas. (Stuttg). 1978, 40:518-531.

Szczeklik A, Gryglewski RJ. Thromboxane A_2 synthesis by platelets of patients with coronary heart disease. International Conference on Atherosclerosis 1978; 597-605.

INTERRELATIONSHIPS BETWEEN RISK FACTORS

Since these Rounds have become much more Grand than was intended, the ending will be mercifully brief, in the form of some overall principles:

1. Based on available data, a large part of the U.S. population is at risk for premature cardiovascular disease (Kannel *et al*, 1976)(Table 44).

TABLE 44

Percent Prevalence of Selected "Risk Factors" in the United States

Age (yr)	Inactivity*	Obesity	Hypertension	Cigarette Smoking	Diabetes	Hyper-cholesterolemia	ECG-LVH*
			Men				
35–44	12.1	12.5	13.5	48.6	1.1	20.2	2.9
45–54	16.9	14.7	18.3	43.1	1.1	25.7	4.8
55–64	21.0	12.5	22.3	37.4	3.3	23.5	10.1
65–74	27.1	12.7	27.1	22.8†	3.2	21.6	7.1
			Women				
35–44	13.3	20.1	8.5	38.8	0.8	12.9	0.9
45–54	19.3	24.2	18.2	36.1	2.9	28.0	3.6
55–64	30.8	30.9	31.2	24.2	3.2	49.7	4.1
65–74	39.0	27.2	47.6	10.2†	6.1	51.0	9.6

* Framingham, Mass.

† Age 65 and over.

Definitions: Inactivity is average oxygen consumption less than 0.30 liter/min (1954–58); obesity is weight 20 percent or more above median (1960–62); hypertension is a blood pressure at least 160/90 (1960–62); cigarette smoking refers to current habits (1970); diabetes is medically treated (1960–62); hypercholesterolemia is a serum cholesterol at least 260 mg/100 ml (1960–62); ECG-LVH is an electrocardiographic pattern of left ventricular hypertrophy (1948–53). Data for 1960–62 come from publications of the Health Examination Survey, series 11, numbers 14 (obesity), 13 (hypertension), 2 (diabetes) and 22 (hypercholesterolemia). Data on cigarette smoking are from the National Center for Health Statistics (unpublished).

2. Though many are at some risk, those in the upper 20% of overall risk will have 50% of the premature CV disease. Those men in the upper 10% will have 62% of the coronaries. Up to 70% of overall risk is related to smoking, hypertension and hypercholesterolemia (Whyte, 1976).

3. Risks are at least additive; additional risk may produce a multiplying effect. Those with any one risk should be more carefully screened and treated for the others. It should be helpful for both physician and patient to ascertain overall risk. An exact number can be found

by using the American Heart Association booklets for coronary and stroke risk. A close approximation for the risk of an MI can be made by multiplying the appropriate relative risk factors shown in Table 45 (Khosla *et al*, 1977). Thus a 48-year-old with a cholesterol of 290, a systolic blood pressure of 165 who smokes 25 cigarettes a day would have this relative risk:

1.36	x	2.20	x	2.80	x	2.40	=	20.2
(age)		(chol)		(BP)		(Smok)		

TABLE 45

RELATIVE RISK FACTORS FOR CORONARY HEART DISEASE (CHD) WITH PREDICTIVE VALUES FOR U.S. POPULATIONS

Age (Years)	Risk of CHD	Cholesterol (mg/100 ml)	Risk of CHD	Systolic Blood Pressure (mm Hg)	Risk of CHD	Smoking (cigarettes/ day)	Risk of CHD
40-44	1.00	<180	0.74	<115	0.73	None	1.00
45-49	1.36	to 229	1.00	to 129	1.00	<5	1.25
50-54	1.84	to 289	1.61	to 159	1.70	to 9	1.56
55-59	2.40	to 299	2.20	to 169	2.80	to 19	1.95
≥60	2.50	≥300	3.00	≥170	5.00	to 29	2.40
						≥30	3.00

4. Individual physicians, working with individual patients, can do much to reverse CV risks. But, in view of the scope of the problem, a society-wide approach is needed. With enough effort, it can work as shown by the Stanford 3 community program (Farquhar *et al*, 1977) and the North Karelia Project (Paska, 1978). But simply screening the masses does little good (Aronow *et al* 1975a) since many physicians do not provide adequate follow-up care and many patients won't follow the advice that is given (Aronow *et al*, 1975b).

For those already affilicted, heart transplants and coronary by-passes will continue to be needed. But preventive medicine to reduce CV risks will do far more to prolong healthy life. To be effective it must start in childhood and involve us all. The broad program suggested by the Royal College of Physicians (Br Med J 1976; 1:881-882) seems an appropriate ending to this attempt to call attention to the meaning of risk factors and the potential for better health by their reduction.

REFERENCES: *Interrelationships between risk factors*

Aronow WS, Allen WH, Cristofaro D et al. Follow-up of mass screening for coronary risk factors in 1817 adults. Circulation 1975; 51:1038-1045.(a)

Aronow WS, Allen WH, Christofaro D. Response of patients and physicians to mass screening for coronary risk factors. Circulation 1975; 52:586-588.(b)

Farquhar JW, Wood PD, Breitrose H et al. Community education for cardiovascular health. Lancet 1977; 1:1192-1195.

Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 1976; 38:46-51.

Khosla T, Newcombe RG, Campbell H. Who is at risk of a coronary? Br Med J 1977; 1:341-344.

Puska P, Virtamo J, Tuomilehto. Cardiovascular risk factor changes in a three-year follow-up of a cohort in connection with a community programme (the North Karelia Project). Acta Med Scand 1978; 204:381-388.

Whyte HM. The relative importance of the major risk factors in atherosclerotic and other diseases. Aust NZ J Med 1976; 6:387-393.

Risk factors and recommendations

Diet—Dietary recommendations for the whole community involve a reduction in the amount of saturated fats and partial substitution by polyunsaturated fats. Where plasma lipid concentrations indicate a particularly high risk, or where other risk factors are concurrently present, the dietary recommendations should be followed more strictly. Widespread screening for plasma lipid levels is not recommended but estimations should be carried out in certain groups known to be at high risk of CHD. Maintaining a desirable weight is important, as obesity is commonly associated with other more potent risk factors for CHD. Weight reduction should be based on a decrease in all the dietary components; sugar and alcohol are recognised as common sources of excess energy intake. A combination of exercise and diet is strongly recommended.

Smoking—Every effort should be made to discourage cigarette smoking, particularly in the young. Doctors and other health workers should set an example, and less harmful methods of smoking should be advised for those who are unwilling to stop.

Blood pressure—Blood pressure should be recorded for every patient, using the opportunities provided by any consultation. In those with even moderately raised blood pressures the control of other risk factors (cigarette smoking, diet, physical inactivity) is important. Treatment of raised blood pressure is at present justified on the grounds of reducing the risk of stroke and other complications, but its effect on CHD risk is not yet established.

Physical activity—Physical activity should be encouraged at all ages and in both men and women. Few people need to consult their doctor before making a graded increase in their physical activity.

Stress—While acute stress may occasionally precipitate a heart attack, it is difficult to prove that chronic stress contributes to the development of CHD. The management of stress, whether it be domestic or occupational in origin, is a normal part of medical practice. Initiative, diligence, leadership, and hard work, especially in young people, should not be discouraged on the mistaken supposition that these qualities are indicators of future CHD.

Diabetes mellitus—Reversal of risk factors should form part of the care of diabetics, and dietary policy for individual diabetics should be determined as much by their plasma lipid concentrations as by the blood sugar response.

Oral contraceptives—Oral contraceptives constitute a negligible risk in women under the age of 40 years who have no risk factors for CHD, but they should be used with caution in women over 40 years, those with a family history of premature CHD, and those who are heavy cigarette smokers (>20/day) or have other risk factors.

(Br Med J 1976; 1:881-882)