Research Related to Risk Factors

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SUMMARY The epidemic of premature coronary heart disease (CHD) in the U.S. and other Western industrialized countries is a result of modern lifestyles and the risk factors related to them. It is scientifically correct to designate habitual eating patterns high in cholesterol, saturated fats, calories as the primary cause of this epidemic. Such diets are responsible for the high prevalence rates in these populations of hypercholesterolemia, an established major CHD risk factor. Additional established major risk factors that enhance coronary proneness in persons and populations with the lipid nutritional-metabolic prerequisites for severe atherosclerosis are hypertension and cigarette smoking. A sedentary lifestyle at work and leisure and incongruent behavior (e.g., the type A behavior pattern) are probable additional adjuvant risk factors in such populations.

Data on the impact of major risk factors in one population enable prediction of risk in other populations. In populations with lifestyles rendering them generally coronary-prone, accurate assessment of CHD risk can be made at least from youth on, probably even in the first decade of life, enabling a preventive public-health strategy that combines efforts to improve lifestyles (diet, smoking and exercise) for the whole population from childhood (primary-habit formation) through middle age, with special concentrated attention to identified very high risk individuals and families.

THE IDENTIFICATION of the major risk factors for atherosclerotic disease — a key research achievement in the last 30 years — is the scientific foundation for prevention. The major established risk factors are a “rich” diet (i.e., diet high in saturated fat, cholesterol, calories, sugars and salt), diet-dependent hypercholesterolemia and hypertension, and cigarette smoking. They are designated major risk factors because their powerful contribution to the etiology of epidemic atherosclerotic disease (particularly premature coronary heart disease [CHD]) is scientifically established, they are common in the population of the United States and other industrialized Western nations and, given their relationship to lifestyle, they may be prevented or controlled.

Detection of the Major Risk Factors

Identification and detection of risk factors proceeds at two levels — for whole populations and for individuals. The first has yielded extensive data on the key factors responsible for the risk status of entire populations, e.g., the high-risk status overall of the American population.

Figure 1 shows one type of research finding in this area: the relationship between dietary high-fat, high-cholesterol animal products and risk of CHD mortality for the populations of whole countries. These are data from the UN Food and Agriculture Organization (FAO) and the World Health Organization (WHO). More than 10 such studies have reported highly consistent data of this kind over the last three decades.1 In terms of the foodstuffs, each point is the mean number of calories from these animal products available daily per person for the specified country for the years 1954–1965, and the CHD mortality rates are for 1973, for the age group 35–74 years, age-standardized. The U.S. is at the high end of the distribution for both variables, along with Finland, Australia and New Zealand. At the low end of the distribution note the position of Japan, unique among the highly industrialized countries both in regard to low intake of lipid-rich animal products and CHD mortality rates. Several correlations between foodstuffs and CHD mortality are high order and highly significant statistically for both men and women.1 When the data on foods from the FAO balance sheets are converted into nutrients, the correlations are statistically significant for dietary cholesterol, saturated fat, total fat, daily calories and CHD mortality for both men and women, with correlation coefficients around 0.5–0.7. National indices for other aspects of lifestyle also relate significantly to CHD mortality rates for both men and women, e.g., average per capita tobacco consumption.

The massive autopsy studies of the International Atherosclerosis Project yield similar data, in this case with the end point of actual severity of coronary atherosclerosis. The rank correlation coefficient between percent calories from fat in the national diet and atherosclerosis reference rank was 0.668; between national patterns of serum cholesterol and atherosclerosis reference rank, 0.755; and between lipid content of the national diets and the national patterns of cholesterol, 0.741.5

Over these decades, study after study of living population samples internationally have yielded similar data.1–7, 8 Among these, the Seven Country Study6–8 and the Ni-Hon-San Study are particularly comprehensive.8–15 Both show significant associations among average dietary lipid intake, mean serum cholesterol level and CHD incidence rates. Ten-year data from the Seven Country Study are just becoming available.8 The differences between the southern European populations, and the northern European and U.S. samples in dietary lipid, serum cholesterol and

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mortality rates are clear-cut. The situation is similar with respect to findings repeatedly recorded for Japanese in Japan vs Japanese-Americans in Hawaii and California, e.g., most recently by the Ni-Hon-San Study.\(^1\)\(^{9-15}\) Data comparing migrant and home country populations show that cited differences among populations internationally in CHD rates are due to differences in sociocultural (i.e., lifestyle) factors, and not to differences in population-genetic susceptibility to the disease (none have been demonstrated). Multivariate analyses show that the relationships between diet-serum lipid and CHD are independent of other major risk factors.\(^6\)\(^{7,15}\)

As to risk assessment of individuals, it is more than 20 years since the publication of the first prospective data from the Albany, Framingham and Los Angeles studies.\(^16\) In the 1958 monograph, Nutrition and Atherosclerosis, the essentials of these early findings were illustrated, and on or about that time the traits were first spoken of as coronary risk factors.\(^3\)\(^{,16}\) Since then confirmatory evidence has accumulated from long-term follow-up of many populations.

The extensive epidemiologic data on the relationship of "rich" diet, hypercholesterolemia, hypertension and cigarette smoking to risk of CHD meet the essential criteria for demonstrating that the associations are indicative of an etiological relationship, i.e.:

1) The associations are strong.
2) The associations are graded in nature.
3) The associations have the necessary temporal relationships in that the risk factors precede the disease.
4) The associations are generally consistent in multiple studies.
5) The associations are independent.
6) There is powerful and accurate predictive capacity, i.e., application of data on risk factors from one population yields good prediction of CHD risk in another population and the individuals in it.
7) The data are coherent, i.e., the epidemiologic data are consistent with findings from other research methods, and reasonable pathogenic mechanisms are known.

As to the the criterion of coherence, I will show only a few sets of data from animal research to illustrate the vast array of evidence from other methods consistent with and confirmatory of the epidemiologic findings. Table 1 shows that an increase in plasma cholesterol supervenes when cholesterol is added to the diet of monkeys at levels less than (groups 1 and 2) or equal to (group 3) those frequently consumed by Americans.\(^17\) This suprervened with use of a semi-purified diet containing a mixture of fatty acids shown neither to raise nor lower serum cholesterol. After 18 months on this diet, arterial intimal thickening was present in all three cholesterol-fed groups, generally proportional to the increase in dietary and plasma cholesterol (fig. 2).\(^18\) For the first two experimental groups, fed cholesterol at levels of 43 and 129 mg per 1000 calories, respectively, these pathologic changes developed although mean plasma cholesterol levels.
TABLE 1. Plasma Cholesterol Changes at Three Levels of Dietary Cholesterol in Semipurified Diet, Adult Rhesus Monkeys

<table>
<thead>
<tr>
<th>Group</th>
<th>Dietary cholesterol (mg/1000 calories)</th>
<th>Plasma cholesterol (mg/dl)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>115 ± 2.5</td>
<td>130 ± 4.6</td>
</tr>
<tr>
<td>2</td>
<td>129</td>
<td>117 ± 2.6</td>
<td>168 ± 4.2</td>
</tr>
<tr>
<td>3</td>
<td>387</td>
<td>115 ± 2.0</td>
<td>392 ± 18.3</td>
</tr>
</tbody>
</table>

*SEM, five animals per group.
Monkeys were fed 600 calories/day, to maintain positive caloric balance.

were within the range found in monkeys fed cholesterol-free diets. This is in accordance with earlier findings in rabbits and chickens. Hundreds of animal studies in a wide range of species — herbivores, carnivores and omnivores, birds and mammals, including many species of nonhuman primates — document the important role of dietary lipid, particularly dietary cholesterol, in atherogenesis. The recent data also show that addition of cholesterol to the diet of primates not only elevates serum total cholesterol, but also induces a change in the distribution of that cholesterol among the lipoprotein fractions. That is, the rise is principally in the serum cholesterol carried by low-density lipoprotein (LDL), rather than high-density lipoprotein (HDL), with a consequent increase in the ratio of circulating LDL to HDL cholesterol. Given the considerable evidence on the atherogenicity, particularly of LDL cholesterol, and the accumulating data indicating that HDL may be antiatherogenic, this effect of dietary cholesterol is particularly important. Moreover, cholesterol feeding induces a change in HDL in both animals and man, with emergence of an HDL subclass that behaves in tissue culture like LDL, suggesting it may itself be atherogenic rather than antiatherogenic.

Hypercholesterolemia and atherosclerosis developed in monkeys fed usual American diets, but were much less marked when a "prudent" human diet of Mediterranean-Far Eastern style (i.e., containing much less cholesterol and saturated fat) was fed. With prolonged, diet-induced hypercholesterolemia, severe atherosclerosis and its major complications (e.g., peripheral gangrene, myocardial infarction and coronary sudden death) have been induced in several species, including nonhuman primates. Hyper tension, a condition not productive of atherosclerosis by itself, has been shown to accelerate and intensify atherogenesis significantly in cholesterol-fat-fed animals (rabbits, dogs, chickens and monkeys), again in accordance with the human findings on the key role of dietary lipid in the multifactorial etiology of this disease. Finally, the data from the animal laboratory are also consistent with the findings on man in regard to the potential for prevention with control of major risk factors. Thus, data on cessation of atherogenesis and regression of lesions as a result of discontinuation of diets high in cholesterol-fat have been reported for many species. The last decade is notable in regard to work on regression in nonhuman primates.

A few other points should be made about assessment of risk. First, clear-cut data are available indicating that accurate risk assessment is possible beginning as early as the second decade of life (and probably earlier). The data abstracted from the Harvard and University of Pennsylvania entrance examinations of several decades ago are highly revealing. A single examination of blood pressure taken in the teens was predictive of CHD risk 20, 30 and 40 years later, as was smoking history and information on weight status (table 2). These habits and traits in youth have synergistic effects on subsequent risk of CHD in middle age.

**TABLE 2. Overweight, Systolic Blood Pressure (SBP) Elevation, Cigarette Smoking and Coronary Heart Disease Mortality Ratio, Harvard and Penn College Entrants**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of entrants</th>
<th>Mortality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>25%</td>
<td>1.4</td>
</tr>
<tr>
<td>SBP ≥ 130 mm Hg</td>
<td>27%</td>
<td>1.6</td>
</tr>
<tr>
<td>Smoking ≥ 10 cigarettes/day</td>
<td>13%</td>
<td>1.6</td>
</tr>
<tr>
<td>Overweight and SBP ≥ 130 mm Hg</td>
<td>7%</td>
<td>2.3</td>
</tr>
<tr>
<td>Overweight and smoking</td>
<td>4%</td>
<td>1.9</td>
</tr>
<tr>
<td>SBP ≥ 130 mm Hg and smoking</td>
<td>4%</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Abbreviation: SBP = systolic blood pressure.

Figure 2. Relation of dietary cholesterol to aortic intimal thickening, measured as area in transverse microscopic sections. Shown are the average areas from preselected sites in individual monkeys, five animals per dietary group.
Table 3. Mortality Ratios for Coronary Heart Disease by Amount of Cigarette Smoking, Men and Women by Age at Entry—6-Year Follow-up, 1,000,000 Persons Study, American Cancer Society

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men mortality ratio</th>
<th>Women mortality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never smoked regularly</td>
<td>1-9 a day</td>
</tr>
<tr>
<td>40-49</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>50-59</td>
<td>1.00</td>
<td>1.59</td>
</tr>
<tr>
<td>60-69</td>
<td>1.00</td>
<td>1.48</td>
</tr>
<tr>
<td>70-79</td>
<td>1.00</td>
<td>1.14</td>
</tr>
</tbody>
</table>

*Rates based on only five to nine deaths.*

At the other end of the age spectrum, data from several large-scale prospective studies show that both cigarette smoking and high blood pressure remain important risk indicators for persons in the seventh and eighth decades of life. Tables 3 and 4 display representative data. The recent report from Framingham indicates that when total serum cholesterol is fractionated into its LDL, VLDL and HDL components, LDL and HDL are significantly related to risk (the former directly, the latter inversely) for elderly people, along with the other major risk factors.

Second, unquestionably, overweight in youth and middle age increases risk of both hypertension and hyperlipidemia. The latest data indicate that, in addition, substantial overweight makes an independent contribution to CHD risk at least up to baseline age 50 years.

Third, recent work by our group, using the Chicago Western Electric Company and Peoples Gas Company data, show that a first good approximation of risk is possible simply, quickly and inexpensively through questionnaire only, focusing on smoking habit, history of hypertension, habitual use of alcohol, weight gain since young adulthood, and family history of premature hypertensive-atherosclerotic disease.

Fourth, the data from international living population and autopsy studies, and the animal-experimental data all show that when the habitual diet is low in cholesterol and saturated fat, severe atherosclerosis and its clinical consequences, particularly premature CHD, are rare, even when such other important factors as hypertension and cigarette smoking are present. The Japanese experience documents this basic conclusion. Therefore, it is scientifically correct to designate diet high in cholesterol, saturated fat, and calories as the primary and essential cause of the epidemic of premature CHD in the U.S. and other Western industrialized countries; the other major risk factors are contributory causes— as the Diet and Coronary Heart Disease Statement of the American Heart Association emphasized. For many people in our country, "rich" diet is both a primary and sufficient cause, unfortunately. For others, this is not the case, and hypertension and/or cigarette smoking add insult to injury, leading to catastrophic disease. Hence the soundness of preventive approaches emphasizing multiple improvements in the norms of human behavior.

Modification of the Major Risk Factors: Research Studies

Significant data are available on modification of the major risk factors on two levels: research studies involving discrete groups and mass changes in the general population. As to the former, extensive studies in the metabolic ward have repeatedly and unequivocally demonstrated—in keeping with the descriptive-epidemiologic and animal-experimental data—that modification of the lipid composition of the diet produces change in serum cholesterol. In particular, reduction in saturated fat and/or cholesterol intake produces reduction in serum cholesterol, an effect that is moderately enhanced by increased polyunsaturated fat intake.

Significant reduction in serum cholesterol by dietary fat modification has also been shown in several trials involving institutionalized groups—e.g., the Los Angeles Veterans Administration domiciliary facility study; the National Diet-Heart Study in Faribault, Minnesota; the Minnesota mental hospital study; and the Helsinki mental hospital study. Similar results have also been reported in large groups of free-living people—e.g., by the Chicago Coronary Prevention Evaluation Program, the New York Anti-Coronalory Club, the five centers working with free-living men in the National Diet-Heart Study, studies of persons with diabetes and the Oslo primary and secondary prevention diet trials, and by MRFIT, all involving middle-aged men. Representative data recorded by the National Diet-Heart Study are shown in figure 3.

As to modification of high blood pressure, the VA trial of antihypertensive drugs showed unequivocally that it is possible to control this risk factor, both its more and less severe forms, by drug combinations. The Hypertension Detection and Follow-up Program has further demonstrated that it is possible to reach out into communities across the country, screen tens of thousands of people in their homes, detect persons with hypertension, evaluate them medically, and enroll them by the thousands into a stepped-care treatment regimen, with high-level, long-term cooperation, adherence and normalization of blood pressure, for younger and older men and women, whites and blacks, lower and higher income, less and more severe hypertensives. For those with the least severe
TABLE 4. Relationship of Blood Pressure to Risk, by Cause: Aging and Elderly Americans

Framingham Study, 18-Year Follow-up
Average annual incidence of cardiovascular events per 1000 population

| Age (years) | Men | | | | Women |
|---|---|---|---|---|---|---|
| | < 90 mm Hg | 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 |

1959 Build and Blood Pressure Study, Society of Actuaries

<table>
<thead>
<tr>
<th>Systolic pressure (mm Hg)</th>
<th>Diastolic pressure (mm Hg)</th>
<th>Ratio (%)* of actual to expected mortality compared with standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men* (age, years)</td>
<td>50-59</td>
</tr>
<tr>
<td>68-82</td>
<td>202</td>
<td>219</td>
</tr>
<tr>
<td>158-167</td>
<td>201</td>
<td>(215)</td>
</tr>
</tbody>
</table>

*With and without minor impairments at examination.
†Age at issue of policy.
Numbers in parentheses indicate mortality ratio based on 10–34 deaths.
Bar indicates fewer than 10 policies terminated by death.

Chicago Stroke Study—3-year risk, men and women, white and black, Ages 65-74 years

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure status*</th>
<th>n</th>
<th>All causes death</th>
<th>CHD death</th>
<th>CVR death</th>
<th>Stroke</th>
<th>Nonembolic brain infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. Rate</td>
<td>No. Rate</td>
<td>No. Rate</td>
<td>No. Rate</td>
<td></td>
</tr>
<tr>
<td>No exclusions</td>
<td>1</td>
<td>1973</td>
<td>361</td>
<td>180</td>
<td>163</td>
<td>80</td>
<td>223</td>
</tr>
<tr>
<td>2</td>
<td>493</td>
<td>100</td>
<td>212</td>
<td>41</td>
<td>90</td>
<td>70</td>
<td>149</td>
</tr>
<tr>
<td>3</td>
<td>224</td>
<td>62</td>
<td>286</td>
<td>29</td>
<td>135</td>
<td>48</td>
<td>220</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>3 vs 1</td>
<td>1.59</td>
<td>1.69</td>
<td>1.98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With exclusions†</td>
<td>1</td>
<td>872</td>
<td>134</td>
<td>154</td>
<td>58</td>
<td>66</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>25</td>
<td>161</td>
<td>11</td>
<td>73</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>12</td>
<td>244</td>
<td>8</td>
<td>163</td>
<td>11</td>
<td>223</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>3 vs 1</td>
<td>1.58</td>
<td>2.47</td>
<td>2.48</td>
<td>2.53</td>
<td>1.65</td>
<td></td>
</tr>
</tbody>
</table>

Death rates adjusted for age-sex-race by analysis of covariance with and without exclusions.
*1—Systolic < 180 mm Hg, diastolic < 90 mm Hg.
2—Diastolic ≥ 95 mm Hg.
3—Systolic ≥ 180 mm Hg, diastolic < 90 mm Hg.
†Excluding anyone with the following conditions at baseline: clinical coronary heart disease, intermittent claudication, definite electrocardiographic abnormalities, peripheral atherosclerosis, diabetes mellitus, high blood urea nitrogen, or gravelly ill in the judgment of the examining physician.

Blood pressure elevations (e.g., average diastolic pressures 90-104 mm Hg), the extensive experience of the Chicago Coronary Prevention Evaluation Program showed that normalization of pressure is possible by nutritional-hygienic means — moderate weight reduction, improved cardiopulmonary fitness through regular, frequent, moderate rhythmic exercise — without uses of drugs (tables 5 and 6). This same approach is apparently effective in controlling blood pressure for hypertension-prone persons, with high-normal average readings (e.g., mean diastolic pressures in the 80–89 mm Hg range), indicating ability to achieve the primary prevention of hypertension by such means in large numbers of people (tables 7 and 8).

As to ability to stop cigarette smoking, the Chicago Coronary Prevention Evaluation Program was one of the early efforts that accrued significant experience in dealing with this habit long-term. In recent years, the 22 centers of MRFIT have shown that it is possible to effect and sustain cessation of cigarette smoking in a sizable proportion of middle-aged, coronary-prone men.

Although their samples were too small to give unequivocal answers as to ability to prevent CHD by modification of risk factors, the early trials — undertaken with all-too-limited resources in the late 1950s — did register meaningful findings in this area as well. For example, the Finnish mental hospital study, using a crossover design, with two 6-year periods for each of its two participating institutions, recorded a 53% lower CHD mortality rate and a 39% lower car-
Table 5. Mean Changes in Six Variables Year-by-year and for All 5 Years, Cohort of 67 Nondropouts with Last Baseline Diastolic Blood Pressure ≥ 90 mm Hg and Relative Weight ≥ 115% Never on Antihypertensive Medication, and with Complete Data for Years 1-5, Chicago Coronary Prevention Evaluation Program

<table>
<thead>
<tr>
<th>Year</th>
<th>Weight (lbs)</th>
<th>Relative weight</th>
<th>Pulse rate (beats/min)</th>
<th>Systolic pressure (mm Hg)</th>
<th>Diastolic pressure (mm Hg)</th>
<th>Serum cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>196.2</td>
<td>130.1</td>
<td>81.2</td>
<td>146.6</td>
<td>95.6</td>
<td>258.3</td>
</tr>
<tr>
<td>1</td>
<td>183.2†</td>
<td>121.4†</td>
<td>77.7*</td>
<td>133.9†</td>
<td>86.2†</td>
<td>226.7†</td>
</tr>
<tr>
<td>2</td>
<td>182.3†</td>
<td>120.7†</td>
<td>77.3*</td>
<td>132.3†</td>
<td>84.8†</td>
<td>232.5†</td>
</tr>
<tr>
<td>3</td>
<td>185.1†</td>
<td>122.7†</td>
<td>77.6*</td>
<td>132.3†</td>
<td>85.8†</td>
<td>233.5†</td>
</tr>
<tr>
<td>4</td>
<td>185.6†</td>
<td>123.0†</td>
<td>76.0</td>
<td>133.0†</td>
<td>85.4†</td>
<td>233.2†</td>
</tr>
<tr>
<td>5</td>
<td>186.4†</td>
<td>123.6†</td>
<td>75.1†</td>
<td>134.9†</td>
<td>87.0†</td>
<td>233.5†</td>
</tr>
<tr>
<td>1-5</td>
<td>184.5†</td>
<td>122.3†</td>
<td>76.7†</td>
<td>133.3†</td>
<td>85.9†</td>
<td>232.2†</td>
</tr>
<tr>
<td>Change, 1–5</td>
<td>−11.7</td>
<td>−7.8</td>
<td>−4.5</td>
<td>−13.3</td>
<td>−9.7</td>
<td>−26.0</td>
</tr>
<tr>
<td>% change, 1–5</td>
<td>−6.0%</td>
<td>−6.0%</td>
<td>−5.5%</td>
<td>−9.1%</td>
<td>−10.1%</td>
<td>−10.1%</td>
</tr>
</tbody>
</table>

*p < 0.01.
†p < 0.001.

Figure 3. (top) Mean percent change in serum cholesterol, all open centers. Baltimore, Boston, Chicago, Minneapolis, and Oakland combined. (bottom) The closed population in the mental hospital in Faribault, Minnesota, lower figure.

Table 6. Change in Weight (%), Pulse (%) and Blood Pressure (%), Cohort of 67 Men with Entry Diastolic Blood Pressure ≥ 90 mm Hg, Relative Weight ≥ 115% Nondropouts, Not on Antihypertensive Drugs, Chicago Coronary Prevention Evaluation Program

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>r=−% Δ wt and % Δ BP, simple and partial</td>
<td>0.306†</td>
<td>0.280*</td>
</tr>
<tr>
<td>r=−% Δ Pulse and % Δ BP, simple and partial</td>
<td>0.182</td>
<td>0.131</td>
</tr>
<tr>
<td>Intercept a</td>
<td>−5.034†</td>
<td>−4.259†</td>
</tr>
<tr>
<td>Coefficient b1—% Δ weight</td>
<td>0.550*</td>
<td>0.982†</td>
</tr>
<tr>
<td>Coefficient b2—% Δ pulse</td>
<td>0.082</td>
<td>−0.007</td>
</tr>
<tr>
<td>Bivariate r</td>
<td>0.330*</td>
<td>0.478‡</td>
</tr>
<tr>
<td>r²</td>
<td>0.109</td>
<td>0.228</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; wt = weight.
*p ≤ 0.05.
†p ≤ 0.01.
‡p ≤ 0.001.

diovascular disease mortality rate for men during their years of serum cholesterol reduction on a fat-modified diet. The double-blind randomized controlled trial in the Los Angeles VA domiciliary facility had similar results, despite the handicap of a study group of median age 65 years with a large proportion of the men having overt signs of arteriosclerotic disease. Evidence of preventive impact of the fat-modified serum-cholesterol-lowering diet was particularly clear-cut for men under age 65 years at entry, with hypercholesterolemia and free of signs of arteriosclerotic disease.

As to the benefits of sustained control of high blood pressure, the VA trial clearly proved efficacy for...
middle-aged men with mean diastolic levels of 115–129 mm Hg (93% reduction in rate of nonfatal plus fatal complications), and for those with mean diastolic values of 105–114 mm Hg (69% reduction).\textsuperscript{65-67} The rate of cerebrovascular disease was dramatically and significantly reduced, and in Americans the majority of strokes are atherothrombotic (not hemorrhagic) in nature, i.e., this particular atherosclerotic disease end point was clearly influenced. For the stratum with the least severe elevation, 90–104 mm Hg, the 45% lower event rate compared with the placebo group was not statistically significant, given the small sample size.

In regard to the VA data, a difference that is not statistically significant is not synonymous with no difference. This also applies to the VA data on coronary events. Although that study was far too small to test ability of antihypertensive drugs to influence CHD as a single, specific end point, the trend of its data are impressively positive, though not statistically significant — a 56% lower rate of sudden coronary death, a 50% lower rate of all coronary fatalities (sudden and nonsudden). The pooled data from four randomized controlled trials of antihypertensive drugs show a 40% lower CHD rate in the treated compared with the placebo group ($p = 0.10$) (table 9).\textsuperscript{65, 66, 74-76}

As to benefit of quitting cigarette smoking before catastrophic illness has occurred, while no data are available from a randomized controlled trial on this matter, several prospective epidemiologic studies have reported impressive data.\textsuperscript{4, 5, 6, 7, 77} Figure 4, from the 15-year follow-up findings of the study of U.S. veterans (originally set up by Dr. Harold Dorn), is representative.\textsuperscript{78, 79} Data from the Coronary Drug Project indicate that even after one or more myocardial infarctions, quitting cigarette smoking still improves long-term prognosis.\textsuperscript{80}

\begin{table}[h]
\centering
\begin{tabular}{lrrrrrr}
\hline
Year & Weight (lbs) & Relative weight & Pulse rate (beats/min) & Systolic pressure (mm Hg) & Diastolic pressure (mm Hg) & Serum cholesterol (mg/dl) \\
\hline
0 & 192.4 & 127.5 & 77.7 & 130.3 & 83.0 & 258.5 \\
1 & 180.8 \dagger & 119.8 \dagger & 74.9* & 123.0 \dagger & 78.6 \dagger & 234.2 \dagger \\
2 & 180.2 \dagger & 119.3 \dagger & 74.5* & 123.0 \dagger & 78.4 \dagger & 237.8 \dagger \\
3 & 181.3 \dagger & 120.2 \dagger & 73.8 \dagger & 123.1 \dagger & 78.8 \dagger & 241.8 \dagger \\
4 & 183.5 \dagger & 121.6 \dagger & 74.0 \dagger & 124.2 \dagger & 80.2 \dagger & 243.7 \dagger \\
5 & 183.4 \dagger & 121.5 \dagger & 74.1 \dagger & 123.8 \dagger & 79.5 \dagger & 244.4* \\
1-5 & 181.8 \dagger & 120.5 \dagger & 74.3 \dagger & 123.4 \dagger & 79.1 \dagger & 240.4 \dagger \\
Change, 1-5 & -10.5 & -7.1 & -3.4 & -0.8 & -3.9 & -18.1 \\
% change, 1-5 & -5.5% & -5.6% & -4.4% & -0.5% & -4.7% & -7.0% \\
\hline
\end{tabular}
\caption{Effect of Antihypertensive Treatment on Occurrence of Major Coronary Events: Data from Four Randomized Controlled Trials}
\begin{tabular}{lrrrrrr}
\hline
Study & Placebo & Drug & \\
\hline
 & No. of patients & No. of events & No. of patients & No. of events \\
\hline
U.S.—VA Coop. Group\textsuperscript{46, 44} & 264 & 16 & 259 & 11 \\
U.K.—Hamilton et al.\textsuperscript{74} & 31 & 3 & 30 & 1 \\
U.S.—Wolff and Lindeman\textsuperscript{28} & 42 & 4 & 45 & 2 \\
U.K.—Coop. Trial\textsuperscript{76} & 58 & 2 & 58 & 1 \\
Total & 395 & 25 & 392 & 15 \\
\hline
\end{tabular}
\end{table}
Modification of the Major Risk Factors in the U.S. General Population

During the last 20 years, expert groups and public leaders have repeatedly advised Americans to pursue better lifestyles, i.e., to modify major risk factors for preventive purposes.1, 41, 43, 81-88 Tables 10 and 11 are illustrative of dietary recommendations.41 The American people have been making changes. U.S. Department of Agriculture data indicate that per capita annual consumption of eggs, dairy fat and lard have decreased significantly (table 12).1, 89, 90 As a consequence, intake of total animal fat is down (fig. 5),91 despite increased consumption of meat, especially beef, so that both cholesterol and saturated fat per day are down modestly. On the other hand, use of vegetable oils and fats is up, and they are being hydrogenated less (e.g., soft margarines, liquid shortenings), so that polyunsaturated intake is up (from about 3.8% to 5.7% of calories) (fig. 6).92 A recent U.S. Department of Agriculture survey shows that a substantial percentage of the American people report altering their eating patterns deliberately for health reasons, to lower weight, serum cholesterol,

Table 10. Dietary Goals for the United States

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 29% 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 polyunsaturated and monounsaturated fats, which should account for about 10% of energy intake each day.
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/day.

Table 11. Changes in Food Selection and Preparation to Achieve the U.S. Dietary Goals

1. Increase consumption of fruits and vegetables and whole grains.
2. Decrease consumption of refined and other processed sugars and foods high in such sugars.
3. Decrease consumption of foods high in total fat, and partially replace saturated fats, whether obtained from animal or vegetable sources, with polyunsaturated fats.
4. Decrease consumption of animal fat, and choose meats, poultry and fish, which will reduce saturated fat intake.
5. Except for young children, substitute lowfat and nonfat milk for whole milk, and lowfat dairy products for high-fat dairy products.
6. Decrease consumption of butterfat, eggs and other high-cholesterol sources. Some consideration should be given to easing the cholesterol goal for pre-menopausal women, young children and the elderly in order to obtain the nutritional benefits of eggs in the diet.
7. Decrease consumption of salt and foods high in salt content.

Table 12. Per Capita Annual Consumption U.S.A., 1940-1974

<table>
<thead>
<tr>
<th>Commodity</th>
<th>1940</th>
<th>1950</th>
<th>1974</th>
<th>Percent change, 1940-1974</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs—no.</td>
<td>319</td>
<td>389</td>
<td>287</td>
<td>-10.0% -26.2%*</td>
</tr>
<tr>
<td>Total milk fat solids—lbs</td>
<td>33</td>
<td>29</td>
<td>20</td>
<td>-39.4%</td>
</tr>
<tr>
<td>Lard—lbs</td>
<td>14</td>
<td>13</td>
<td>3</td>
<td>-78.6%</td>
</tr>
<tr>
<td>Shortening, margarine, other edible fats and oils</td>
<td>18</td>
<td>26</td>
<td>50</td>
<td>+177.8%</td>
</tr>
<tr>
<td>Poultry—lbs</td>
<td>17</td>
<td>25</td>
<td>51</td>
<td>+200.0%</td>
</tr>
<tr>
<td>Beef—lbs</td>
<td>55</td>
<td>63</td>
<td>117</td>
<td>+112.7%</td>
</tr>
</tbody>
</table>

Correspondingly, evidence is available from many sources — e.g., long-term studies in Albany, Chicago, Framingham, Minneapolis, Tecumseh; the NHES-HANES surveys of 1960-1962 and 1971-1974, respectively, on random national samples of the U.S. population; the mass screening efforts of MRFIT and the LRC — that the mean serum cholesterol level of the population is down, e.g., for middle-aged males by about 7%,6, 36, 95-98 The American people are seeking to achieve the Dietary Goals for the United States (tables 10 and 11).41 The LRC data indicate that this is particularly so for the more educated.

Among adults, especially adult men, the proportion smoking cigarettes has decreased — down since 1964 by 25% for men, 11% for women.99-101 The serious
problem among teenagers, especially teenage girls, and young women, and the high-level average per capita consumption (the highest in the world) should not blind us to the achievements already recorded despite all-too-modest resources.

In addition to the changes in eating and smoking habits, millions of Americans have also become more active in their leisure time (table 13). Statistics on trends of sales of bicycles, tennis rackets, running shoes, and so on, are confirmatory, though we have no population data on trends of cardiopulmonary fitness of the U.S. population.

Finally, there is the major set of achievements in regard to hypertension, sparked by a cooperative effort that has developed since the launching of the High Blood Pressure Education Program in 1973. The equation of 5 years ago — ½ × ½ × ½ — half the hypertensives undetected, half of those detected untreated, half of those treated still hypertensive — no longer holds. Instead of only one-eighth (12.5%) of the hypertensives detected, treated and controlled, that figure is now up around 50%.68, 101, 102

Real progress has been made in modification of risk factors, although much remains to be done to achieve critical mass in terms of the whole population and control of the epidemic. This is the challenge of the next decade in regard to prevention.

The Decline in Mortality Rates

Finally, as we move forward to meet this challenge, no better — no more encouraging — foundation exists than the data on the decline in mortality rates: Coronary rates down 24% from 1968–1976 for persons age 35–74 years; stroke rates, 33%; all cardiovascular disease death rates, 25%; all-causes mortality rates, 17%.104–106 More than 200,000 lives are being saved annually in this age group, almost 100,000 as a result of the decline in CHD mortality alone.104–106

These three decades have indeed been exciting and fruitful.

Acknowledgements

It is a pleasure to acknowledge the cooperation of the author's senior colleagues in the long-term investigations. The author is also most grateful to the nurses, nutritionists, programmers, technicians, clerks and secretaries who contributed to this research. It is also a pleasure to express appreciation to the many Chicago organizations giving invaluable cooperation in the cited research efforts.

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References


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**Table 13**. Reported Exercise by Americans, 1977

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Who exercises?</th>
<th>Who jogs?</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>47%</td>
<td>11%</td>
</tr>
<tr>
<td>Men</td>
<td>50%</td>
<td>16%</td>
</tr>
<tr>
<td>Women</td>
<td>45%</td>
<td>7%</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>60%</td>
<td>22%</td>
</tr>
<tr>
<td>30–49</td>
<td>47%</td>
<td>10%</td>
</tr>
<tr>
<td>50 +</td>
<td>38%</td>
<td>4%</td>
</tr>
<tr>
<td>College educated</td>
<td>59%</td>
<td>17%</td>
</tr>
<tr>
<td>High school</td>
<td>47%</td>
<td>11%</td>
</tr>
<tr>
<td>Grade school</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>Professional and business</td>
<td>56%</td>
<td>13%</td>
</tr>
<tr>
<td>Clerical and sales</td>
<td>57%</td>
<td>10%</td>
</tr>
<tr>
<td>Manual</td>
<td>45%</td>
<td>12%</td>
</tr>
</tbody>
</table>

Source: Gallup poll.


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Mechanical Function of the Heart and Its Alteration During Myocardial Ischemia and Infarction

Specific Reference to Coronary Atherosclerosis

H. J. C. Swan, M.D., Ph.D.

SUMMARY  Altered regional mechanical myocardial performance is an early, sensitive marker of myocardial ischemia, and can be estimated in man with reasonable accuracy. Identification, localization and quantification of abnormalities in mechanical performance can be used to predict the presence of coronary artery disease. Testing techniques that have little or no effect on diagnostic efficiency must be replaced with more sensitive indicators of ischemia. If experimental data are validated by findings in human subjects, accurate identification of regional wall motion changes during test conditions should prove to be a powerful marker of ischemia. To be of value, a diagnostic test must strongly increase the frequency of identification of subjects with a high probability for the presence of coronary artery disease in an otherwise low-prevalence population, and of those with known disease who are at the highest risk for complications including myocardial infarction or death.

THE CLINICAL CONSEQUENCES of atherosclerosis of the coronary arteries are primarily the result of alterations in myocardial blood flow or distribution and the effects on the mechanical and electrical properties of the heart. Important anatomic coronary artery disease may be present and readily identified by coronary arteriography or at autopsy without the manifestations of significant adverse effects in the patient during his lifetime. Ischemic heart disease is the proper term when coronary artery narrowing is severe enough to cause a reduction or redistribution of blood supply under conditions of stress or even at rest. Luminal alteration also may result from changes of vasomotor tone or from the adherence of formed elements of the blood to normal or abnormal intimal surfaces. Hence, the degree and location of luminal wall narrowing are as critical in ischemic heart disease as the presence of intraluminal coronary atherosclerosis.

While a reasonable measure of the degree of narrowing necessary to cause reduction of coronary blood flow is possible in the experimental animal, its quantification by coronary arteriography in man is still open to considerable error; this is particularly true at intermediate degrees of coronary arterial narrowing. For example, few coronary arteriographers would disagree about angiograms demonstrating normality or minimal (<20%) luminal restriction on the one hand, or 90–99% narrowing on the other. The 40–70% range of diameter reduction is where the greatest variability appears to exist. The data of Gould et al.

1 indicate that the critical degree of narrowing is at about 80% diameter reduction. Values above this level are consistently associated with limitation of blood flow and values below it cause flow limitation only under conditions of increased demand. Coronary vasomotor tone and coronary spasm are of increasing interest as potentially important factors in the modulation of the degree of narrowing in some patients with 60–75% organic obstruction. Spasm alone is a primary factor in a minority of patients. There is increasing speculation that permanent or
Research related to risk factors.

J Stamler

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