Diet and Atherosclerosis

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Because of the statistical establishment of elevated blood lipids as a risk factor in the development of atherosclerotic heart disease, most of the attempts to regulate blood lipids by diet are centered on the fat in the diet. The levels of blood lipids and the course of experimental atherosclerosis can be affected by other dietary components such as type and amount of protein, carbohydrate, and nonnutritive fiber. Interaction among the dietary components further affects serum lipids and atherosclerosis. (Am J Pathol 84:615–632, 1976)

LONG-TERM STUDIES[1,2] have clearly shown that elevated serum cholesterol levels are one of the principal indications of a susceptibility to atherosclerotic coronary heart disease (ASHD). Hurxthal[3] and Page[4] and their co-workers have demonstrated that blood cholesterol levels may have a predictive value in individuals. In addition to serum cholesterol levels, serum triglyceride levels have been shown to be correlated with incidence of ASHD,[5,6] as have the serum lipoprotein levels.[7,8] However, as Shanoff[9] has pointed out, many of the factors that are highly correlated with the etiology of ASHD in a given population may not tell much for any individual.

The implication of the serum lipids in the development of ASHD has made them the focus of attempts to moderate the course of this disease or to prevent it. The thrust of most of the dietary studies has been to evaluate the premise that high levels of serum lipids are due primarily to increased intake of dietary fat and that reduction or alteration of the lipid in the diet will lower the levels of lipids in the blood and, hence, reduce the risk and incidence of ASHD.

The purpose of this exposition is not to expand on the lipid hypothesis, which is well established, but rather to show that the serum lipids (and the course of ASHD) can be affected by dietary components other than lipid. It is essential that the total diet be examined, as there are few susceptible populations subjected to the monotony of a single-component diet.

The one aspect of the American diet which has borne the brunt of the attack has been lipid. The general thesis has been that since the beginning

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of this century the amount and type of fat in our diet has changed and that this change underlies the increase in coronary heart disease. However, *everything* in the diet has changed. Friend [10] has summarized the changes in the availability of nutrients in the United States since 1909. Some of her data and those of Gortner [11] and Rizek *et al.*[12] are summarized in Table 1. It is evident that several important changes have occurred in the American diet since 1909. While protein availability has not changed much, the ratio of animal to vegetable protein has doubled. Carbohydrate availability has fallen by 21%, and the level of dietary fiber has fallen by 30% since 1909 [11] and by 47% since 1880.[13] Fat availability has increased by 26% since 1909; the intake of animal fat has fallen by 7% and that of vegetable fat has increased by 181%. The ratio of polyunsaturated to saturated fatty acids was 0.21 in 1909 and 0.43 in 1974. Cholesterol availability was 509 mg in 1909 to 1913 and 556 mg in 1970. The peak intake was 578 mg in 1957 to 1959 and the average (1909 to 1970) was 540 mg. In the period 1900 to 1960, the death rate from heart disease rose from 130/100,000 to 355/100,000.

Masironi [14] compared diet and cardiovascular death rates in a number of countries between 1955 and 1965 and found no clear trends. Thus, in the United States there was a 4% increase in death rate and a decrease in saturated fat intake and in total calories. In Switzerland, with a 5.5% increase in death rate, the total intake rose by 28% and the saturated fat intake by 18%. Finland, which showed a 30% increase in death rate, exhibited a 34% increase in saturated fat intake and a 123% increase in sucrose consumption. In Yugoslavia, the death rate increased three- to fourfold, the saturated fat intake fell by 26% but that of sucrose almost tripled. The data suggest that many factors in the diet play a role in ASHD; this exposition proposes to touch on each dietary class.

Table 1—Trends in Per Capita Nutrient Availability*

Year	Calories	Protein		Carbohydrate (g)	Fat		Fatty acids (g)		
		Total (g)	A/V		Total (g)	A/V	Sat	18:1	18:2
1909-1913	3490	102	1.06	492	125	4.88	50.3	51.5	10.7
1925-1929	3466	94	1.20	476	135	2.69	53.3	55.2	12.5
1935-1939	3270	90	1.27	430	135	2.85	52.9	54.5	12.7
1947-1949	3230	95	1.78	403	141	2.88	54.4	58.0	14.8
1957-1959	3140	95	2.06	374	143	2.41	54.7	58.2	16.6
1965	3160	96	2.19	371	145	1.94	53.9	58.8	19.1
1972	3320	101	2.37	381	158	1.64	55.9	63.1	23.3
1974	3350	101	2.26	388	158	NA	56.0	62.9	24.2

A/V = animal origin/vegetable origin; NA = not available, Sat = saturated.
* After Friend,[10] Gortner,[11] and Rizek *et al.*[12]

Lipid

The occurrence of cholesterol in animal fat and the lower iodine value of fat of animal origin, together with various epidemiologic data, suggest that cholesterol-lowering diets should be rich in polyunsaturated fats. A number of primary prevention studies [15-17] have reported lowered serum cholesterol levels in men fed diets high in unsaturated fat. The number of myocardial infarctions were also lower in the test group. A secondary prevention trial in Oslo [18] showed that men placed on a diet high in unsaturated fat had fewer myocardial infarctions, but a similar trial in England [19] was without effect. Could the rest of the diet have played a role?

In animals there is ample evidence that diets containing cholesterol and saturated fat are more atherogenic than similar diets in which the fat is unsaturated.[20,21] Saturated fats can even be atherogenic in semi-purified diets containing no cholesterol,[22-24] but as we shall see below, the observed effect is not due to the dietary fat alone.

However, unsaturation of a fat is not a guarantee of a beneficial effect. In 1957, Ahrens [25] drew a relationship between iodine values of dietary fats and serum cholesterol levels. Compared to corn oil, fats such as lard, palm oil, butter, cocoa butter, and coconut oil were significantly more cholesteremic. Peanut oil yielded cholesterol levels similar to those observed with corn oil. When administered as part of an atherogenic diet, however, peanut oil was found to be inordinately atherogenic for rats,[26,27] rhesus monkeys,[28,29] and rabbits.[30] A mixture of fats whose fatty acid spectrum resembled that of peanut oil minus arachidic and behenic acids was no more atherogenic than corn oil,[30] but subsequent studies showed that randomization of peanut oil significantly reduced its atherogenicity.[31] Randomization is an interesterification process whereby the component fatty acids of a triglyceride are evenly distributed among the three glycerol positions. The experiments are summarized in Table 2. Randomization does not affect the atherogenicity of butter or lard. These findings suggest that more remains to be learned concerning fat structure and its effects on cholesterol metabolism and atherosclerosis. When added to a cholesterol-free, semi-purified diet, peanut oil is less atherogenic than either butter or coconut oil but is significantly more atherogenic than corn oil.[32]

Protein

Ignatowski [33] provided the first clear demonstration that diet affected the course of atherosclerosis. He fed meat, milk, and eggs to rabbits and observed atherosclerotic lesions in their aortas. Ignatowski concluded that

Table 2—Influence of Peanut Oil and Other Fats on Experimental Atherosclerosis in Cholesterol-Fed Rabbits*

Fat	No. of animals	Serum cholesterol (mg/dl)	Average atheroma†	
			Aortic arch	Thoracic artery
Coconut oil	44/45	1360	2.15 ± 0.16	1.67 ± 0.14
Peanut oil	98/106	1483	1.89 ± 0.10	1.35 ± 0.08
PGF‡	73/76	1650	1.57 ± 0.10	1.11 ± 0.09
PGF + AB§	31/31	1723	1.40 ± 0.12	0.94 ± 0.09
Peanut oil-R¶	31/31	1833	1.31 ± 0.12	1.05 ± 0.10
Corn oil	100/106	1548	1.52 ± 0.10	1.05 ± 0.07

* All diets contain 2% cholesterol and 6% fat.

† Graded on a scale of 0–4.

‡ Prepared by blending 10% cottonseed oil, 55% olive oil, and 35% safflower oil. Fatty acid composition resembles that of peanut oil less arachidic and behenic acids.

§ PGF interesterified with arachidic and behenic glycerides. Fatty acid composition was identical with that of peanut oil.

¶ Randomized (autointeresterified) peanut oil.

the animal protein had injured the aortic wall. However, all of the substances which he fed contained cholesterol, and the demonstration by Anitschkow and Cholatow [34] that diets containing cholesterol in vegetable oil could produce atherosclerosis shifted research emphasis towards cholesterol and other lipids.

In comparing epidemiologic data relating to diet and heart disease, Yudkin [35] and Yerushalmy and Hilleboe [36] observed in 1957 that the incidence of ischemic heart disease could be correlated with intake of animal protein as readily as with intake of fat.

The data in Table 1 also suggest that the trend of increasing coronary mortality in the United States parallels the increasing ratio of animal to vegetable protein. The protein level of the American diet has been virtually unchanged since 1909. Although there has been little work reported on the effects of dietary protein on serum cholesterol levels and atherosclerosis, the available data suggest that both type and amount of protein may be important. In 1920, Newburgh and Squier [37] reported that rabbits fed a meat diet exhibited some atherosclerosis after 4 weeks; if the diet contained casein (30 g/day), aortas were normal at 10 weeks but did become atherosclerotic by 11 months. A later experiment [38] showed that rabbits fed powdered beef at a level sufficient to give a 27% protein diet showed atheromatous lesions after 1 year; no lesions were observed at 26 weeks. If the diet contained 36% protein, early atherosclerosis could be seen by 2 months. The only cholesterol present in the diet was that contained in the dried beef. Rabbits fed the 27% protein ingested about 30 mg of cholesterol daily. Meeker and Kesten [39,40] fed rabbits 250 mg of cholesterol daily in diets containing 38% casein or 39% soy protein or a

basal diet. The soy protein diet gave the highest serum cholesterol levels but the lowest incidence and severity of atherosclerosis. When the rabbits were fed only 60 mg of cholesterol daily, the basal diet was more atherogenic than the soy protein diet. In the absence of cholesterol only the casein diet was found to be atherogenic.

Nath *et al.*[41] fed rats cholesterol and different levels of casein and wheat gluten and found that the former protein was the more cholesteremic. When it was 40% of the diet, casein gave an average cholesterol level of 431 ± 39 mg/dl, whereas the level in rats fed 40% wheat gluten was 210 ± 8. Similar differences were observed at other levels of protein.

Lofland and his co-workers [42-45] fed pigeons and squirrel monkeys diets in which the fat and the amount and level of protein and cholesterol were varied. The results of one experiment are summarized in Table 3. They show that serum cholesterol levels vary with the type of fat and level of protein, but in general, the high-protein diets were more atherogenic than the low-protein diets. In other experiments,[43] they found that in the absence of dietary cholesterol a 15% protein diet was more atherogenic than either 30% or 5% protein diets, but when 0.25% cholesterol was added, the 30% protein diet became the most atherogenic. These findings held true whether the dietary fat was corn oil or coconut oil. When squirrel monkeys were fed high- or low-protein diets, the severity of aortic and coronary atherosclerosis was similar in the absence of cholesterol, but the high-protein diet was more than twice as atherogenic if cholesterol was added to the diet. Computerized statistical analysis of the data from all these experiments revealed no independent variable.

Table 3—Influence of Fat and Protein on Atherosclerosis and Serum Cholesterol Levels in Pigeons*

	Wheat gluten		Casein	
Fat	High	Low	High	Low
Butter				
SC	419 ± 23	398 ± 22	472 ± 22	399 ± 47
AI	3.5 (100%)	4.3 (60%)	5.1 (89%)	3.1 (71%)
Corn oil				
SC	492 ± 32	676 ± 96	345 ± 41	404 ± 31
AI	5.7 (78%)	3.5 (56%)	5.2 (100%)	3.1 (56%)
Crisco				
SC	495 ± 45	377 ± 37	577 ± 98	643 ± 56
AI	4.3 (85%)	2.5 (58%)	3.5 (89%)	0.7 (55%)
Margarine				
SC	442 ± 32	387 ± 32	375 ± 24	242 ± 21
AI	2.0 (60%)	1.3 (36%)	3.0 (73%)	0.4 (42%)

High = 30% of calories, low = 8% of calories, SC = serum cholesterol (mg/dl), AI = atherosclerotic index; prevalence in parentheses.

* After Lofland *et al.*[44]

Strong and McGill [46] fed baboons diets high (20% of calories) or low (8% of calories) in casein, high (0.5%) or low (0.01%) in cholesterol and containing 40% of calories as saturated (iodine value, 53.0) or unsaturated (iodine value, 108.9) fat. Thus, there were eight dietary combinations: high cholesterol plus saturated or unsaturated fat and high or low protein and low cholesterol–saturated or unsaturated fat–high or low protein. In only one set (high cholesterol–saturated fat) did the low-protein diet lead to more aortic sudanophilia than did the high-protein diet. In the other three sets, the high-protein diet was more sudanophilic and cholesteremic. Statistical analysis of the cholesterol data showed significant interactions between lipid parameters and cholesterol and a significant second order interaction of protein with fat and cholesterol.

In chickens, low-protein diets enhance experimental atherosclerosis,[47] and high-protein diets appear to have a protective effect.[48,49] Protein level does not affect spontaneous atherosclerosis in chickens.[50]

Munro *et al.*[51] found that rabbits fed 1% cholesterol plus 30% casein had more cholesterol in their adrenals (45%) and liver (148%) than did rabbits fed 1% cholesterol plus 8% casein. Serum cholesterol levels in the 30% protein group were 820 mg/dl compared with 605 mg/dl in the 8% protein group. Atheromata in the high protein group were slightly more severe (2.1 versus 1.7).

Howard *et al.*[52] found that replacing casein with soya flour inhibited the hypercholesteremia and atherosclerosis observed in rabbits fed semi-purified diets.

Hodges *et al.*[53] carried out an experiment in 6 volunteers who were fed diets containing various ratios of simple and complex carbohydrates. Their source of protein was mixed at the beginning and end of the experiment, but was soybean protein during the study. The average cholesterol level was almost 300 mg/dl at the beginning of the study, dropped to about 200 mg/dl during the test period and rose to the beginning levels when the diet reverted to a mixture of animal and vegetable protein.

Walker *et al.*[54] reported that young women ingesting a diet containing 50 g of vegetable protein had lower serum cholesterol levels than did women eating 50 g of animal protein.

Carroll and Hamilton [55] studied the effects of defatted protein (30%) on serum cholesterol levels in rabbits. They fed a number of proteins of animal and vegetable origin and found the latter type to be uniformly less cholesteremic (Table 4). Of interest in these experiments are the observations that potato starch can completely vitiate the hypercholesteremic effect of casein and that butter or corn oil plus either casein or soy protein

yield lower cholesterol levels than when either protein is fed in a low-fat diet.

The foregoing suggests the need for awareness of possible interactions when assessing the effects of diet. Caution should be exercised before attributing cholesteremic or atherogenic effects to any one component.

Carbohydrates and Fiber

Yudkin [35,56,57] has put forward the hypothesis that sucrose consumption is of central importance to the etiology of ASHD. His views are based on a correlation of coronary heart disease mortality with sugar intake in certain countries. Yudkin's hypothesis has been subjected to criticism.[58-60] With regard to Yudkin's sucrose hypothesis and other theories implicating other single dietary components, it is well to remember Ashton's [61] caution against any direct causal interpretation of dietary correlations.

Dietary carbohydrate affects serum triglyceride levels [62-64] but appears to have little effect on serum cholesterol levels.[65] Grande [66] has reviewed the effects of carbohydrates on serum lipid levels and emphasized the complexity of the findings and the difficulties in interpretation. One should separate effects of simple carbohydrates from those of the more complex ones. Among the latter, sucrose and fructose are generally considered to be more triglyceridemic than glucose, although there are conflicting data. Anderson [67] has reviewed some of these data.

Complex carbohydrates contain various levels of nonnutritive fiber, and

Table 4—Effect of Protein on Plasma Cholesterol Levels of Rabbits*

Protein	Plasma cholesterol (mg/dl)
Animal	
Whole egg extract	232
Skim milk powder	228
Lactalbumin	212
Casein	204
Fish protein	166
Beef protein	158
Pork protein	112
Raw egg white	100
Vegetable	
Wheat gluten	82
Peanut protein	82
Pea protein	46
Soy protein	40
Fava bean protein	32

* After Carroll and Hamilton.[54] Groups of 4 to 7 rabbits were fed a diet containing 30% protein and 1% fat for 28 days.

the fiber, rather than the nature of the digestible sugar, may account for the reported differences.

About 20 years ago, two groups of investigators [22,23] reported that they had established atherosclerosis in rabbits by feeding them a diet free of cholesterol but high in saturated fat. Collation of the literature available at that time [68] indicated that the addition of saturated fat to a stock diet did not render it atherogenic, but that when the same fat was part of a semi-purified diet, that diet was hyperlipidemic, hyper-β-lipoproteinemic, and atherogenic for rabbits. Clearly, the fat alone was not the determinant of atherogenesis, and it was suggested that the type of carbohydrate or fiber present in the diet might be important.[68] An experiment was carried out in which a semi-purified diet containing 40% dextrose and 14% hydrogenated coconut oil was compared with a diet containing 85% lipid-free residue obtained by extraction of laboratory ration, 1% vitamin mix, and 14% hydrogenated coconut oil.[69,70] The semi-purified diet was much more cholesteremic and atherogenic. Moore [71] carried out an experiment using a semi-purified diet containing 20% butter and varied the non-nutritive element of the diet (wheat straw; cellulose; cellophane; or cellophane:peat, 14:5). The cellophane-containing diet was most cholesteremic and atherogenic, followed closely by the cellulose diet. The wheat straw diet was least atherogenic.

Experiments with different types of carbohydrates in the semi-purified diet [72,73] indicated that fructose and sucrose were much more atherogenic than glucose. Lactose was not atherogenic when a component of a cholesterol-free diet; although lactose (30%) plus cholesterol is severely atherogenic for rabbits.[74] Our data [72,73] are summarized in Table 5.

Semi-purified diets containing different carbohydrates have been fed to baboons.[75] Fructose, sucrose, starch, and glucose are equally cholesteremic. Glucose and starch raised triglyceride levels by 43%, and fructose and sucrose raised them by 55 to 72%. The most sudanophilic carbohydrate was fructose and the least, glucose. A fructose-rich semi-purified diet was found to be atherogenic for vervet monkeys.[76] The mechanism of action of this type of diet appears to involve decreased synthesis of bile acid, which results in reduced conversion of cholesterol in the liver and its diversion to the serum.[75,77,78]

When different carbohydrates are fed to animals on a cholesterol diet, sucrose is more cholesteremic than glucose for rabbits [79,80] or chickens.[81,82] Lang and Barthel [83] fed 0.5% cholesterol and 66% sucrose or dextrin to three different species of monkeys. In *Macaca mulatta*, dextrin was more cholesteremic and atherogenic, but aortic cholesterol was higher in the sucrose-fed monkeys; in *Cebus albifrons*, dextrin gave more intimal pro-

Table 5—Effects of Carbohydrates on Atherosclerosis in Rabbits Fed Cholesterol-Free, Semi-Purified Diets*

Carbohydrate	Serum cholesterol (mg/dl)	Average atheromata	
		Aortic arch	Thoracic artery
Experiment 1† (33 wks)			
Glucose	209 ± 31	1.1	0.9
Sucrose	310 ± 66	1.9	1.0
Starch	640 ± 97	2.3	1.2
Hydrolyzed starch	400 ± 77	1.7	1.0
Experiment 2‡ (40 wks)			
Glucose	451 ± 102	1.1	0.6
Fructose	922 ± 231	2.1	0.9
Sucrose	520 ± .19	1.7	1.2
Lactose	329 ± 144	0.6	0.4
Starch	532 ± 152	1.5	1.2

* All diets contain 40% carbohydrate, 25% casein, 15% cellulose, 14% hydrogenated coconut oil, 5% salt mix, and 1% vitamins.
† Kritchevsky *et al.*[72]
‡ Kritchevsky *et al.*[73]

liferation of the coronary arteries but no higher cholesterol level; in *Macaca arctoides* there was no difference between the diets.

Most semi-purified diets contain cellulose as the bulking agent. Substitution of alfalfa in rat diets will inhibit cholesterol absorption,[84] and any number of mucilaginous gums will lower serum and liver cholesterol levels.[85,86] Pectin will inhibit cholesterol-induced atherosclerosis in rabbits,[87] chickens,[88,89] and pigs.[90]

The absence of atherosclerosis in many primitive peoples has been attributed to the high level of fiber in their diets.[91-95] Keys *et al.*[96] found that cellulose did not lower cholesterol levels in man but that pectin did. Bran has also been shown to have no effect on serum lipids in man.[97] Leguminous products such as bengal gram [98] have a marked hypocholesteremic effect in man (Table 6).

Experiments in which dietary sucrose has been replaced by some form of starch result in reductions in serum cholesterol levels ranging from 2 to 11%. Some of these are summarized in Table 7.

Interaction between dietary fiber and protein can affect atherosclerosis. We have fed rabbits semi-purified diets containing cellulose, sucrose, and casein or soy protein. The casein diet is more cholesteremic and atherogenic. Substitution of wheat straw for the cellulose does not affect cholesteremia but reduces atherogenicity of both diets. When the fiber

Table 6—Influence of Bengal Gram on Lipid Metabolism in 20 Patients*

Diet	Serum cholesterol (mg/dl)	Fecal steroids (mg/24 hr)		
			Bile acids	
		Neutral	Cholic	Deoxycholic
Basal	123 ± 23	272	59	105
High fat (10 wks)	206 ± 20	455	74	163
High fat + Bengal gram (55 wks)	160 ± 24	470	106	200

* After Mathur *et al.*[98]

source is alfalfa, cholesterol levels are reduced in both groups and atheromata are of equal severity.[106]

Trace Elements

The possibility that trace elements may affect atherosclerosis is usually met with tolerant disinterest. While the data may not be as compelling as those involving the major dietary components, they carry a respectable epidemiologic imprimatur. In view of the increasing evidence of the importance of dietary interactions, trace elements may be important for their possible role in effecting those interactions.

Water softness has been implicated as an etiologic factor in cardiovascular disease.[107-109] Water hardness has also been negatively correlated with sudden death from arteriosclerotic heart disease or other causes.[110,111]

Table 7—Effect of Exchanging Sucrose for Starch on Serum Cholesterol Levels of Normolipemic Patients

Study	Starch	No. subjects	Duration (days)	Calories exchanged (%)	Change in serum cholesterol (mg/dl)	*P*	Reference
1	Fruit, vegetables, legumes	28	42	17	−18 ± 2.2	<0.01	99
2	Rice	6	25	19	− 6 ± 8.5	NS	100
3	Bread, potatoes	12	21	17	− 4 ± 5.7	NS	101
4	Leguminous seeds	12	21	17	−19 ± 5.2	<0.01	101
5	Cereals, potatoes*	18	28	23	−11 ± 3.1	<0.01	102
6	Cereals, potatoes†	18	28	23	−10 ± 4.2	<0.05	102
7	Cereals, potatoes‡	18	28	23	− 8 ± 3.4	<0.05	102
8	Bread	15	14	35	−13 ± 8.1	NS	103
9	Bread	15	14	35	−24 ± 7.0	<0.01	103
10	Wheat starch§	10	30	40	− 9		104
11	Wheat flour	12	14	16	− 7 ± 4.4	NS	105
12	Mixed vegetables	12	14	16	−22 ± 3.8	<0.01	105

* Coconut oil.
† Olive oil.
‡ Safflower oil.
§ Studied in women only.

Table 8—Negative Association Between Cardiovascular Mortality and Water Quality*

Country	No. of studies	Main characteristics of water
Canada	2	Hardness
Finland	2	Dissolved solids, conductivity
Ireland	1	Hardness
Italy	2	Hardness
Japan	2	Hardness, alkalinity
Netherlands	1	Hardness, Ca
Sweden	1	Hardness, Ca
UK	5	Hardness, Ca, Mg
USA	8	Hardness, Ca, conductance, α and β radioactivity

* After Masironi *et al.*[113]

Masironi and his co-workers [112,113] have summarized the findings in the United States as well as internationally; a summary of their findings is presented in Table 8. The correlation seems to be especially strong for hypertensive heart disease.[112]

Muss [114] related water quality in each of the contiguous United States with deaths from cardiovascular disease. Table 9 shows that there is a general correlation; thus, the six states with the highest death rates range

Table 9—Correlation of Male Cardiovascular Death Rate With Water Hardness*

State	Death rate	Water hardness	State	Death rate	Water hardness
South Carolina	1	47	Montana	25	18
Maryland	2	36	Alabama	26	33
Nevada	3	14	Arizona	27	5
New Jersey	4	28	Mississippi	28	40
Illinois	5	12	Texas	29	15
Louisiana	6	30	Missouri	30	24
New York	7	35	Oregon	31	48
Pennsylvania	8	27	Wisconsin	32	11
North Carolina	9	41	West Virginia	33	26
Rhode Island	10	42	Tennessee	34	29
Massachusetts	11	44	Idaho	35	19
Georgia	12	39	Kentucky	36	25
California	13	20	Utah	37	7
Florida	14	17	Oklahoma	38	16
New Hampshire	15	43	Iowa	39	6
Virginia	16	31	Minnesota	40	22
Delaware	17	32	Arkansas	41	38
Indiana	18	4	Colorado	42	23
Michigan	19	21	Wyoming	43	9
Connecticut	20	45	Kansas	44	8
Ohio	21	13	Nebraska	45	2
Washington	22	37	South Dakota	46	1
Vermont	23	24	North Dakota	47	10
Maine	24	46	New Mexico	48	3

* After Muss.[114]

from 12th to 47th in water hardness, whereas the six states with the lowest death rates range from 1st to 10th in water hardness.

Voors [115] suggests that the beneficial effect of water hardness should be viewed in the light of the high positive correlation between water hardness and lithium level.

Schroeder [116] has suggested that chromium deficiency is a factor in atherosclerosis. His suggestion is based on analyses of chromium in tissues of Americans of different ages and comparision with data from tissues available from abroad. In the United States, chromium levels in aortas and livers fall with increasing age, and atherosclerotic aortas may contain no chromium at all. Chromium is essential for glucose and lipid metabolism [117] and its lack may increase atherosclerosis. The best sources of dietary chromium are brown and raw sugars, millet, beets, and peas.

Klevay [118] has raised the possibility that coronary heart disease can be explained in the ratio of dietary zinc to copper, a high Zn/Cu ratio being detrimental. He has reviewed the epidemiologic literature and concluded that the Zn/Cu ratio is more closely associated with risk than any factor save cholesterol. Klevay has shown [119] that there is a high Zn/Cu ratio in high fat foods and suggests that the efficacy of dietary fiber [120] lies in the fact that the phytic acid of fiber ties up excess zinc. In experiments with rats,[121] Klevay has shown that conventionally reared rats fed a diet with a Zn/Cu ratio of 5 have cholesterol levels of 141 mg/dl, whereas the cholesterol level is 180 mg/dl if the ratio is 40. It will be interesting to follow this work through a series of dietary experiments. Human autopsy material and tissues from animals maintained on various atherogenic diets should yield important clues relating to the Zn/Cu hypothesis.

In summary: There is much to be learned about the effects of dietary interactions on serum lipid levels and atherosclerotic heart disease. Although fat intake has been most commonly indicated as the causative agent in heart disease, other dietary components can affect serum lipids. Attempts to correlate death rates from ASHD with cholesterol intake lead to some anomolous data.[122] Thus, in 1955 to 1956 the USA had the highest death rate (750/100,000) and an average cholesterol intake of 600 mg/day. Finland, with the second highest death rate (680/100,000), showed a cholesterol intake of only 310 mg/day. France, with a daily cholesterol intake of 350 mg had a death rate of only 140/100,000. These data were for men aged 55 to 59.

The amount and type of carbohydrate and protein affect serum cholesterol levels and atherosclerosis. Dietary fiber may also affect lipid levels. At this writing, the term *fiber* covers a variety of substances containing various amounts of celluloses, hemicelluloses, pectins, and lignins. Full

understanding of the effect of fiber will come when we know the composition of the fiber present in each food and how each of these components affect metabolic processes. Finally, there is evidence that trace elements may exert an important effect on lipid metabolism. And not only may the elements *per se* be important but the ratio of one to another must be considered.

Recently, Armstrong *et al.*[123] have tried to relate commodity consumption and dietary practices in 30 countries to mortality from ischemic heart disease. They found positive correlations with gross national product, calories, animal and total protein, fat, sugar, meat, eggs, coffee, tea, and cigarettes. Negative correlations with cereals and vegetables were discerned. There were numerous first and second order correlations. They conclude: "These results suggest that associations identified in this type of investigation should be interpreted with great caution and need not necessarily reflect causal relationships but rather suggest avenues along which further research might proceed." Amen.

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