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Detection and treatment of the coronary-prone individual

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DETECTION AND TREATMENT OF THE CORONARY-PRONE INDIVIDUAL

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Coronary Heart Disease as a Major Cause of Death

The purpose of this paper is first to review the factors associated with the development of Coronary Heart Disease, which includes primarily the study of blood lipids, and secondly to evaluate the methods available to combat the development of this disease.

The significance of Coronary Heart Disease as a cause of death can be revealed by a glance at some statistics. The number of deaths in the United States in 1958 due to Heart Disease at the different age groups are subdivided into the major etiological classifications and compared with the total number of deaths during the same period of time. These figures are listed below:

Table I [1]

Age	All Causes	Heart Disease	Rheumatic Heart Disease	Arteriosclerotic Heart Disease	Hypertensive Heart Disease
Total	1,647,886	637,246	17,990	461,373	73,634
Under 5	131,350	519	-	-	-
10-19	-	-	245	-	-
20-29	27,341	1,752	644	518	112
30-39	48,400	13,620	1,734	4,898	776
40-49	104,024	33,052	3,264	23,737	3,129
50-59	200,922	81,025	4,274	61,490	8,361
60-69	342,501	152,699	3,970	117,574	16,991
70-79	418,248	195,331	-	143,426	24,035

Table II

Percentage of All Deaths
caused by Arteriosclerotic Heart Disease in 1958

Age Group	Percent	Age Group	Percent
30-39	10%	50-59	33%
40-49	23%	60-69	34%

According to the National Office of Vital Statistics in the United States in 1959, approximately one-half of all deaths were caused by diseases of the cardiovascular system, or 509 per 100,000 population, and of this, 300 per 100,000 pop. was due to arteriosclerosis and degenerative heart disease, and 269 of this due to arteriosclerotic heart disease including the coronary artery. Vascular lesions affecting central nervous system accounted for 108 per 100,000 and this was primarily due to cerebral hemorrhage, embolism and thrombosis. The other cardiovascular deaths were split up between rheumatic heart disease, hypertensive heart disease, and other non-specific diseases of the heart arteries and veins. It is interesting to note that in 1959, 38% of the deaths were caused by diseases of the cardiovascular system and in 1950, this accounted for 37% of the deaths; however the specific causes of cardiovascular deaths changed from 1950 to 1959 ~~because~~ there was a decrease in deaths assigned to cerebral hemorrhage, and hypertensive heart disease, and an increase in the deaths from cerebral embolism and thrombosis and arteriosclerotic heart disease especially of the coronary arteries.[2] Death from arteriosclerosis, especially of the coronary arteries, is on the rising end of the plank in about every age group in white males and in the age group of 65 and over, and has shown a 20% increase in the last ten years; whereas hypertensive heart disease has gone down 38% during that same ten years.[3] From this we can see that Coronary Artery Disease is a major cause

of death in the United States and the incidence is apparently increasing.

How long has Coronary Artery Disease been a major cause of death? Heberden, in 1768, in his classic account of Angina Pectoris had 20 cases, and Sir William Osler was admitted to the Royal College of Physicians before he had seen a case in hospital or in private practice.[4] From clinical experience, for example, Dr. P.D. White feels that there has been a definite increase from 1925 to 1950 in the incidence of the disease which is more than just due to increased length of life and better diagnosis.[5] Consequently the clinical disease was apparently uncommon prior to the Twentieth Century and has steadily been increasing during this century.

An example of the increase in the death rate of Coronary Heart Disease can be seen from statistics compiled in England and Wales where the rate per million population was 47 for males age 50 in the period 1921 to 1930, 576 from 1931 to 1939, and 916 from 1940 to 1945. The pattern was similar for females but involving only about one-fourth as many deaths. There was also a similar increase in the incidence at other age levels; however in the middle age group, 40 to 55, the male death rate was increasing more rapidly than females, whereas in the older age groups the position was reversed.[4]

An analysis was made of the necropsy records of the London

Hospital where the coronary arteries as well as the myocardium have been routinely examined since 1907-08. Some 6,000 reports from these years to 1949 relating to both sexes ages 30 to 69 show a seven-fold increase in the number of Coronary Heart Disease deaths and they suggest that coronary thrombosis and myocardial infarct were rare before World War I and have since become common.[6]

Before one can accept the fact that, for example, the annual mortality due to Coronary Heart Disease in Great Britain has increased from 27-47/million in 1915-25 to 1,650/million in 1956, one must analyze these statistics very carefully. The reason for this increase may be the fact that people are living longer, the changing fashion in death certification, or better diagnosis. This increased awareness of the possibility of Coronary Artery Disease is not without its hazzards, because a study in Scotland found the clinical diagnosis of myocardial infarction correct on only 54% of 214 autopsy cases and in 19% of 266 other autopsy cases myocardial infarction was not revealed until autopsy. The diagnosis of myocardial infarction was wrong twice as often as the omission to make the diagnosis.[7]

Another hindrance in unraveling the trend of mortality stems from the radical changes introduced in 1949 in procedures and classifications used for recording the causes of deaths. Some statistics before and after this date can't be compared. Before 1949, coronary disease when certified jointly with chronic diseases, such as

diabetes, nephritis, and carcinoma, was not considered the primary cause of death. However with the introduction of the Sixth Revision of the International List of Causes of Death in 1949, the certifying physician is required to indicate the underlying disease to which the death should be ascribed. Also clinicians have come to accept a broader classification of arteriosclerotic heart disease as more significant for classification than the diagnosis of coronary artery disease. Therefore 30% of the increase in coronary heart disease from 1940 to 1955 could be accounted from by the greater proportion of persons at the older ages. Another 40% of the increase could be ascribed directly to the changes in procedures and classification. Part of the other 30% may have been due to the acceptance of a broader concept of coronary disease, better diagnosis, and increased usage of the term Coronary Artery Disease in certifying causes of death.8

The traditional compilation of statistics on causes of deaths have proven of value in the past when public health was chiefly concerned with infectious diseases. Now with the predominance of chronic diseases these same type of statistics may be inadequate. A diagnosis of Coronary Heart Disease in a living person, may be made on the basis of an acute myocardial infarction with a history of pain, lab, and ECG findings; an old infarct with just ECG findings; angina pectoris with or without ECG evidence; or heart failure due to numerous small infarcts with ECG evidence. The diagnosis in

those that die after showing clinical findings, or those who die of sudden death presumably due to acute coronary occlusion, are determined by the findings of atheromatous plaos, or thrombii in coronary vessels. The significance of the pathological findings is dependent upon the amount of occlusion and the resultant change in the corresponding myocardial tissue. This is given different significance by different pathologists, and comparisons of post mortem findings without uniform diagnostic criteria are difficult to interpret, and unfortunately at present there is no national or international standard nomenclature for such findings in Coronary Artery Disease. Then with this varied information the pathologist or physician puts down what he thinks is the cause of death and the statistician gets this information and compiles it. The problem is that all the signs and symptoms, and pathological findings are lumped in the statistical evaluation into arteriosclerotic heart disease including the coronary arteries, without rigid clinical or pathological basis for the diagnosis.

However before these statistics are disregarded without any consideration it must be remembered that the true incidence of disease is not known for any country, and fine distinctions can't be drawn, but major differences can be drawn. The objection to vital statistics on the ground that autopsies often disagree with the cause of death overlook two points and that is 1) Autopsies involve only a fraction of deaths, and are usually obtained on

problem cases rather than on cases where there is little question, and 2) Disagreements are not really very great, because in comparing autopsy findings with original death certificates in 1,889 deaths in twelve upper New York state hospitals there was full agreement in 72% of 276 deaths certified due to arteriosclerotic heart disease. Disagreement on the frequency of this cause of death was only 3%.9

Consequently, in evaluating the statistics concerning Coronary Heart Disease one must be cognizant of the fact that there may be some error in the statistics and that they may not reveal the true picture, but at present they are the only tool we have for measuring the incidence of the disease, and the statistics will generally reveal the trend of the incidence of disease.

Pathophysiology of Coronary Heart Disease

The possibility of some ambiguity in the pathological diagnosis of atherosclerotic heart disease prompts us to investigate the meaning of atherosclerosis. Atherosclerosis refers to the intimal fibrosis and lipoidosis of the vessel involved. The commonly accepted pathogenesis involved in the development of the clinical disease is as follows. Atherosclerosis involves the left coronary artery, and for some unknown reason this is complicated by intimal hemorrhage and or thrombosis which occludes the vessel. If this occurs acutely without adequate collateral circulation the myocardium distally is infarcted giving rise to the term myocardial infarction, and and then to the clinical syndrome of myocardial infarction. There are variations of this process, because if the occulsion occurs gradually or if there is sufficient collateral circulation, the distal myocardium will only become ischemic, instead of necrosed, and this ischemia will occur only when an increased load is put upon the heart, resulting in myocardial insufficiency and the clinical syndrome is termed angina pectoris. Also the manifestations will vary as to the site of occlusion, because if the occlusion is

distal, then only a small area will be infarcted and may or may not lead to symptoms. A series of such small infarcts may proceed without symptoms, may be distinguished only with ECG, and may eventually involve enough myocardium by the resulting fibrosis to cause heart failure. Conversely if the occlusion is proximal a large area of

the myocardium may be infarcted resulting in the syndrome of myocardial infarction or sudden death.

There has been an argument going on concerning which occurs first, the atherosclerosis or the thrombosis? The advocates of the thrombosis hypothesis say that a mural thrombus is formed which becomes covered with endothelium, incorporated into the vessel wall where it is organized and forms a fibrous thicking of the intima. In most instances before organization is completed fatty changes make their appearance sometimes with softening and ulceration and even calcification. Therefore they advocate that the atherosclerosis is the result of initial thrombosis. Consequently if this is true this would have important bearing on the etiology, because instead of combating those factors associated with atherosclerosis, which has primarily been directed at lipids, the studies would be directed toward something in the blood which allows the coagulation to proceed.[10]

A study in England by Dr. Morris showed a substantial decrease of advanced coronary atheroma as defined by the report of calcified lesions in the arteries between 1908-13 and 1944-49. The decrease was seen in all the relevant sex, age and pathological categories studied. Implications are that coronary thrombosis and heart disease may not be simple and direct functions of the atheroma.[6]

For this study we will presume that both processes are occuring in the development of Coronary Heart Disease. By the term Coronary

Heart Disease we are referring to coronary atherosclerosis, coronary thrombosis, with or without myocardial infarction as the pathological diagnosis accompanying the clinical manifestations of myocardial infarction, ECG evidence of myocardial infarction only, angina pectoris with or without ECG evidence, sudden death, and heart failure as a result of multiple small infarcts and fibrosis. These entities would be appropriately lumped under the inclusive term -- arteriosclerotic heart disease (ASHD).

History of Coronary Heart Disease and the Relationship of Cholesterol

How long have Physicians been aware of Coronary Heart Disease? In 1912, at the time that Dr. Herrick of Chicago described the clinical features of sudden obstruction of the coronary arteries, it was known that obstruction of the left coronary led to sudden death. It was also known at that time that sclerosis of the coronary produced necrosis of the myocardium leading to aneurysm rupture or dilatation of the heart, and they knew that angina pectoris was related to the coronary artery as was cardiac arrhythmias. However it was not realized until this time that large coronary arteries could be occluded without resulting death, at least not immediately. However before they could say this they established that the coronaries were not end-arteries with merely capillary anastomosis, but by dissection and injection they found

significant anatomical anastomosis; and they showed that such anastomoses were of functional value. Then they described the type of patient affected as being over middle age, usually with previous angina, the acute occlusion producing more severe pain, possibly with radiation, weak rapid pulse, decreased blood pressure, rales in the lungs, occasional dyspnea and cyanosis, occasional palpable liver, clear mind with no apprehension after relief of pain, and pericarditis. In his cases death resulted in all cases several days after the onset of symptoms. They revealed by autopsy usually sclerotic vessels with thrombosis totally occluding at the narrowest area and with the resultant softening of the heart. Consequently it was not until 1912 that the syndrome of myocardial infarction was recognized, and it was felt that at that time the etiology was sclerosis and/or thrombosis of the left coronary artery.11 This disease which was first recognized clinically in 1912 is now the commonest cause of death in the United States.

The process of arteriosclerosis and more specifically atherosclerosis had been recognized by pathologists much earlier than clinical syndrome of myocardial infarction although it hadn't been correlated with the clinical syndrome. Lesions of arterial intima were described in 1804 by Scarpa and as early as 1841 Vogel observed cholesterol in the atherosclerotic lesions. Windaus in 1910 analyzed diseased aortas and reported six times as much cholesterol in atherosclerotic aortas as in normal aortas. Anitschkow and

Chalatow in 1913 produced atherosclerosis in rabbits by feeding the animals large quantities of cholesterol. In the 1930's there was an air of skepticism about this relationship. Duff questioned Anitschkow's rabbit experiments producing atherosclerosis by feeding cholesterol, and he maintained that the rabbit is a herbivorous animal and under normal circumstances does not ingest animal cholesterol, thus when an increased amount of cholesterol is given, they have no way of handling it.[12]

In the 1940's by altering lipid metabolism by feeding cholesterol, creating hypothyroidism, or feeding diet deficient in sulfhydril containing amino acids atherosclerosis was produced in all lab species. However it was noted that rabbits developed cholesterosis when fed cholesterol and this was not present in the atherosclerosis in humans, consequently skepticism again arose regarding the experimental simulation of atherosclerosis. However later they were able, by feeding small quantities of cholesterol to rabbits and chickens for long periods of time, to produce minimal hypercholesterolemia without organ, skin, tendon cholesterosis, yet lesions developed in the aorta and coronary vessels.[13] This experimental work along with the fact that there was a higher incidence of atherosclerosis in association with conditions which give rise to high cholesterol levels in man such as familial hypercholesterolemia, myxedema, diabetes mellitus, nephrosis, and Cushings

syndrome, and a low incidence of atherosclerosis in those conditions which are known for their low serum cholesterol levels such as cachexia, hyperthyroidism, Addisons disease, and liver disease, led to the hypothesis that an increased serum cholesterol was associated with an increased incidence of coronary atherosclerosis and thus an increased incidence of myocardial infarction.

Elevated Blood Cholesterol and Coronary Heart Disease

In studies of the distribution of serum cholesterol in serum of patients with coronary heart disease and controlled groups, it has been repeatedly shown that cholesterol values are distributed over similar ranges in both groups but the distribution curve is definitely skewed in favor of high levels in coronary heart disease patients.[14] The correlative studies relating an elevated serum cholesterol in Coronary Heart Disease patients have been for the most part positive, however a study undertaken in 1936 by Lande and Sperry did not conclude that an increase in blood cholesterol was associated with an increase in atherosclerosis. They did autopsies on people who had died a sudden death, in which there was no evidence in any organ of pathological change other than that associated with the fatal injury or atherosclerosis of the blood vessels. The autospy was carried out soon after death, and unclotted blood was taken from the heart and the aorta and analyzed for cholesterol. The cholesterol levels were correlated well with

the cholesterol in a study of healthy men. The comparison supported the view that no significant change in the antemortem constitutional level of total cholesterol occurred after death. In 123 persons who had died suddenly there was no correlation between concentration of the cholesterol in the blood and the lipid content of the aorta. Since the lipid content of the aorta is correlated with the degree of atherosclerosis their conclusion was that there was no correlation with the serum cholesterol and atherosclerosis.[15]

Most studies have revealed an elevation of cholesterol levels in myocardial infarction patients as compared to the normal people evaluated, but the relationship has varied according to age. For example, 1569 adult patients, 149 with a history of old myocardial infarction, and 349 with no evidence of myocardial infarction were evaluated for serum cholesterol. In males with definite evidence of myocardial infarction the cholesterol levels were about the same as the normals in the age groups of 60 and above. The elevation of cholesterol in those afflicted over the normals in the 51-60 age group were barely statistically significant, however the cholesterol levels were elevated significantly in those with evidence of myocardial infarction in those ages below 50. In female patients with myocardial infarction the cholesterol levels were significantly elevated over the levels of the normals at all age levels. Interestingly, a normal cholesterol (under 250 mg%) was found in 12% of the myocardial infarction patients.[16]

There have been studies done showing the elevation in the serum cholesterol in those patients with myocardial infarction remains elevated over a considerable length of time. A study was performed on 15 patients with coronary atherosclerosis and 15 controls. Thirteen of the 15 new patients with coronary atherosclerosis had well documented coronary infarcts and two others had typical angina pectoris and the patients were not included until 6 weeks after the myocardial infarct. Serum cholesterols were done on these people for two years, a total of 914 determinations. The results revealed the controls had a range of 214-334 mg%, mean of 254 mg% with a standard deviation of 8.7; and in the coronary heart disease patients the range was 308-499 mg% with a mean of 355 mg% and a standard deviation of 24.8. This study emphasized the constancy of cholesterol level from day to day, and month to month.[17] It must be mentioned however, that there is evidence to indicate that the level of cholesterol in certain individuals may vary widely within a matter of hours, and that rapid fluctuation of serum cholesterol may be induced in some people by modifying certain aspects of their environment. Whether or not there is a transient isolated fluctuation in the serum cholesterol with time, it is evident that the overall mean cholesterol values over a period of time is significantly elevated in the Coronary Heart Disease patients compared with the normals.

There have been studies relating an increase in the serum

cholesterol level to psychological stress placed upon the individual. Classic study revealed an elevation in the cholesterol in medical students prior to examinations, and the implication was that the stress and strain of modern day living was causing an increase in the blood cholesterol level and thus predisposing the individual to Coronary Heart Disease. However, in a recent study in Cleveland involving medical students this relationship of the elevation of blood cholesterol to the stress of examinations did not hold true.[18]

Another correlation has been made between body build, serum cholesterol and Coronary Heart Disease. A study was done on 97 Coronary Heart Disease patients under age 40, 146 controls, and 97 matched controls in age, body build, weight, ancestry and occupation. The average cholesterol in the control was 224 mg%, in the matched group 241 mg%, and the Coronary Heart Disease patients 286 mg%. It was the opinion of this study group that the Coronary Heart Disease occurred primarily in mesomorphs. Serum cholesterol was higher in mesomorphs by 30 mg%. The matched control group differed as much from the regular control group in body build as did the Coronary Heart Disease group. They found a greater percent of mesomorphs in the matched group as compared with the controls, as well as an increase in the cholesterol, consequently they felt that as the degree of mesomorphy increaes so does the potential for Coronary Heart Disease.[12]

Cholesterol level is also elevated significantly in certain hereditary diseases. There is a metabolic disease which is characterized by a definite increase in blood cholesterol and is inherited as an incomplete dominant and called familial hypercholesterolemia.[19] In this condition there is a definite increase in the incidence of myocardial infarction and angina; in fact it occurs in 43% of those affected with this disease. However in this disease the blood cholesterol elevation appears to be endogenous rather than exogenous and thus not influenced by diet. It is associated with xanthoma tuberosum, xanthoma planum, and xanthelasma. The actual incidence of this disease in the population is not known, but it is relatively rare.[20] Familial hyperlipemia is another genetically transferred disease associated with an endogenous elevation of the blood cholesterol, along with the characteristic elevation of triglycerides, and 34% of those with the disease are afflicted with Coronary Heart Disease.[21]

It has also been shown that those who habitually engage in strenuous physical activity have a lower serum cholesterol than those with sedentary occupations. Later we shall discuss the important elevation of the serum cholesterol determined by percentage of fats in diet, amount of saturated fatty acids, and cholesterol in the diet. Therefore serum cholesterol may be influenced by age, sex, time, stress, body build, heredity, diet, physical activity, and diseases such as diabetes mellitus, nephrosis, and hypothyroidism.

Physiology and Biochemistry of Cholesterol

We have been examining the serum cholesterol values in the pathological state of Coronary Heart Disease and it behooves us to examine the evidence concerning the normal variation of serum cholesterol value with respect to age and sex. In the newborn infants the average serum cholesterol is 35 mg% and from 0 to 10 days it rises to 130 mg%. From age one to puberty there is essentially no change, and after that it depends on sex and dietary intake. In the male from puberty to age 30-35 there is a steady increase in the serum cholesterol.[22]

A study was done on medical students at Johns Hopkins from 1948 to 1957 evaluating serum cholesterol. Ninety-two percent of the 612 students ranged between 150 mg%-299 mg%, with a mean of 228 mg% with a standard deviation of 43. The values were similar for males and females, and the ages included were from 19 to 31. In this study the average cholesterol increased 2.88 mg% per year.[23] This implies a similar increase in both sexes with age in this age group of 20 to 30. However from age 35 on, the trend is less clear. Some say it advances with age to 60, and others say that the cholesterol does not steadily increase. There is some evidence that men reach the highest cholesterol levels between ages 50-54, and then it stabilizes or decreases. It has been found that the cholesterol levels in normals between ages 20-29 was over 260 mg% in 5% of those studied and the proportion over 260 mg% increased

in each decade until age 50, and then was stable until age 70 at which time it decreased.[24] Among well people under 50, men show higher average levels than women. In the women the cholesterol levels gradually increases in the premenstrual years but at a lower level than in men. However after age 50 it increases at the same rate and on the same level corresponding to men.[25] Also in the female there is a premenstrual rise, and a mid-cycle decline which corresponds to a decrease and an increase in the blood estrogen levels respectively, and during pregnancy there is a hypercholesterolemia which is maximum during the 31-32 weeks.[22]

Before we can consider the pathological significance of cholesterol we must understand some basic facts concerning the biochemistry of cholesterol. Cholesterol in the blood is present in two forms: the free form and the esterified form with long chain unsaturated fatty acids. Cholesterol is hydrophobic and therefore must be present in plasma with some constituent that makes it water soluble. Consequently the cholesterol present in plasma is united with a phospholipid-lipoprotein complex.[22] The cholesterol present in plasma is derived from two sources: the exogenous source which is the cholesterol absorbed from the intestinal tract in the presence of fatty acids, pancreatic enzymes, and bile salts, and the endogenous source which is the synthesis of cholesterol occurring primarily in the liver. The precursor is acetyl-coenzyme A which is a product of glycolysis and is con-

verted through the following series of chemical reactions to cholesterol: Acetyl coenzyme A -- mevalonic acid -- squalene -- desmosterol -- cholesterol. The cholesterol synthesized in the liver may 1) enter the blood stream, 2) be converted to steroid hormones, 3) be excreted as bile salts which is the primary method of cholesterol catabolism, and 4) be deposited under abnormal conditions in various tissues.[26] Also some cholesterol may be synthesized in practically all tissues, and as a result of this there appears to be no need to transport cholesterol via lipoprotein complex because peripheral tissues can synthesize their own.[12]

The concentration of cholesterol in the blood is the result of cholesterol ingestion and cholesterol synthesis related to degradation and excretion. The principal products of cholesterol degradation are the bile salts which along with some cholesterol are excreted with bile into the intestinal tract. Some of both are absorbed. Cholesterol is decreased by weight loss, diarrhea, fever, exercise, thyroid hormone, estrogen, nicotinic acid, and sitosterol, and is elevated by rapid gain in weight, cortisone, ACTH, and testosterone.[22]

Lipoproteins

In the search for a relationship between an elevated serum cholesterol and Coronary Heart Disease, a greater understanding of lipid metabolism was established, and with the development of better techniques of chemical analysis, other lipid factors were implicated in this relationship. Lipoproteins, the complex with which cholesterol travels in the blood, were analyzed by paper electrophoresis, and it was found that the beta component contained more cholesterol than the alpha component, and that an elevation of beta liprostein was associated with an increased insidence of coro nary artery disease. Both the alpha and beta lipoproteins contain proteins, triglycerides, phospholipids (which includes fatty acids, phosphate radical and a nitrogenous base), cholesterol and non-esterified fatty acids, the proportions of each being different in each case. These lipoproteins were further subdivided by means of the ultracentrifuge according to their density. Generally the alpha lipoproteins are the high density ones and the beta lipoproteins the low density lipoproteins. Because of the possible relationship between the elevated beta lipoproteins and Coronary Heart Disease a further subdivision was desirable. Consequently with the ultracentrifuge the low density lipoproteins were subdivided into factors according to density. The S_f 10^4-10^5 or chylomicrons which have the highest density of the beta lipoproteins form a cream layer at the top of the centrifuge tube, and are composed of

1% protein and 99% lipid which are largely triglycerides. These chylomicrons prevail in the blood after a fatty meal and are the initial vehicle for the transport of exogenous fat. This component is cleared from the blood by lipoprotein lipase. The next fraction S_f 20-400 is a lower density lipoprotein containing mostly triglycerides and is the primary vehicle for carrying endogenous triglycerides. The next lower density lipoprotein S_f 12-20 contains both triglycerides and cholesterol. The lowest density lipoprotein is the S_f 0-12 fraction, and this contains mostly cholesterol, and it comprises the largest part of the beta lipoproteins in serum.[27]

First they related the S_f 12-20 lipoprotein increase with Coronary Heart Diseases, but this was not as significant as they had hoped. For example, in one study the lipoprotein patterns were evaluated in 107 normal Cleveland executives for seven years. Of these, 12 developed myocardial infarcts and 6 developed angina. Impressive was the lack of change in the lipoprotein determination. Of 18 who developed evidence of Coronary Heart Disease, 5 had S_f 12-20 greater than 75% of the normals, and the others were in the normal range.[28] Dr. J.W. Gofman developed a combination of the low density beta lipoprotein components called the atherogenic index, determined by the formula $.1(S_f\ 0\text{-}12) + .16\ (S_f\ 12\text{-}400)$, which was more consistently elevated in Coronary Heart Disease than either of the beta lipoprotein fractions alone or cholesterol alone, and even showed promise of being of predictive value; but its determination was complicated and costly.

Phospholipids

Because phospholipids as well as the lipoproteins are necessary to keep cholesterol soluble in the blood, the phospholipid level in blood was implicated as being significant in Coronary Heart Disease. Consequently the cholesterol/phospholipid ratio was studied; the rational being that if the ratio were increased there would be an insufficent amount of phospholipid to maintain cholesterol in solution and therefore possibly contribute to the prodess of atherogenesis. The study revealed that in a significant number of people affected with Coronary Heart Disease the ratio was elevated in the presence of a normal serum cholesterol. However the determination of the serum phospholipids is a laborious procedure and not practical.[29]

Triglycerides

In the study of lipoproteins it was found that the elevation of the S_f 20-400 fraction containing primarily triglycerides was significant in coronary artery disease. The S_f 0-12 which contain primarily cholesterol is elevated in Coronary Heart Disease when the cholesterol is also elevated however this is found in only a small number of patients, and it may be due to a specific but uncommon derangement of cholesterol metabolism. Consequently because of the elevation of the S_f 20-400 lipoprotein fraction in Coronary Heart Disease, and since this fraction contains primarily

triglycerides, the study of triglycerides was pursued. It was found that the elevation of the S_f 20-400 with a concomitant elevation of triglycerides and either a normal or elevated cholesterol, and with a slight to marked turbidity of serum was the commonest abnormality in Coronary Heart Disease.[24]

The study of the triglycerides in comparison with cholesterol was done primarily by Dr. M.J. Albrink at the University of West Virginia starting in 1959. In a study of 100 patients with an age range of 21 to 78 with a documented history of myocardial infarction and suitable controls of comparable ages, blood was drawn before breakfast and analyzed for cholesterol and triglycerides. Of the patients with myocardial infarction the cholesterol exceeded 269 mg% in 18% of the patients and in a small percent in those in the control. The triglycerides were elevated above 5.5 milliequivalents/liter in 70% of those affected. Despite the small numbers in each decade, the differences between the means of the normals and those with myocardial infarcts were significant at the 5% level, at least, in all decades studied.[30]

In 115 male patients with a history of myocardial infarction 6 of 43 under age 50 had a serum cholesterol over 260 mg% and normal triglycerides, and only one of 72 over age 50 had this finding. Sixty-four of 72 or 89% over age 50 had triglyceride levels over 5 milliequivalents, and only about 50% had an elevated cholesterol.[24] The relationship between increased cholesterol

levels and Coronary Heart Disease appeared to be significant only in people under age 50, whereas the triglyceride levels were more significant in those over age 50.

The prevalence of increased triglyceride levels in the normal population with the prevalence of Coronary Heart Disease has been correlated. The prevalence rate of Coronary Heart Disease of the age group 30 to 40 is 5/1000, and at age 50 it is 36-46/1000. Four percent of a given middle-aged population has diagnosed Coronary Heart Disease at a given time.[31] The study revealed in the supposedly normals studies that in the 20 to 29 age group there were 5% with serum triglycerides over the 5 milliequivalent/liter, in the 40 to 69 age group there were 40% over the 5 level, and over 70 there were only 15% over the 5 level. Now if we can assume that those with the definite increase in the triglyceride level after the myocardial infarction had an actual elevation before, then we can see that possibly the segment of the population with the elevated triglyceride level at the different age groups accounted for those affected at the different age levels since the relative number, or prevalence corresponds. However to be diagnostic of Coronary Heart Disease susceptibility a serum component survey as a criterion must have certain requirements: 1) the critical concentration must be surpassed by most patients with Coronary Heart Disease, 2) the critical concentration must be surpassed by that proportion of the normal population of a given age who

may have or may be expected to have Coronary Heart Disease, 3) the normal population must not have the attribute in the concentration above the critical value.[31]

The first requirement has been met because the triglyceride level is usually elevated in Coronary Heart Disease. With respect to requirement number two, the triglyceride levels in normal men were increased above normal in 4% over age 40 keeping with the proportion which might be expected to be harboring the disease in whom overt manifestations will eventually develope. The triglyceride level was observed to increase with age, but not in all, because there was a tendency for the serum triglyceride level over 70 to be similar to the concentration of the normal persons of age 20 to 30, and this suggests that by 70 most persons with high serum triglycerides have died. Consequently this study suggests that an increased triglyceride level above 5.5 milliequivalents/liter or 175 mg% may be related to the development of Coronary Heart Disease.

Another dimension with respect to the triglyceride level is the fact that excess triglyceride concentration in plasma may accelerate blood clotting, inhibit fibrinolysis, interfer with oxygen uptake, impair myocardial blood flow, and caused aggregation and adhesiveness of red blood cells.[32, 33]

The serum triglycerides for these studies were analyzed as follows: The blood was first analyzed for total fatty acids after hydrolysis, and also for total cholesterol and lipid phosphate.

The triglyceride fatty acids were then estimated by subtracting the fatty acids attributable to cholesterol esters and phospholipids from the total fatty acids.[30] Another procedure consists of selective quantitative extraction of triglycerides from the plasma, complete saponification of triglycerides, oxidation of glycerol forming formaldehyde, and the colorimetric estimation of formaldehyde.[34] With the exception of chromatographic techniques all routine determinations of triglycerides are based on the estimation of the difference between total lipid and sum of cholesterol, cholesterol esters and phospholipids. From this it can be seen that this procedure is lengthy, requires considerable technical skill and is subject to considerable error.

Comparing the technique utilized for the analysis of triglycerides with that used for estimating cholesterol, it can easily be seen that although there are many procedures for the estimation of cholesterol, they are all more easily performed and require less time than the triglyceride determination. For example the microtechnique for the analysis of serum total cholesterol involves mixing .1 ml of serum with 4 ml of $FeCl_3$, filtering after 2 to 3 minutes, adding H_2SO_4 and reading in a spectrophotometer.[35]

Fat Tolerance

Still another factor implied in association with Coronary Heart Disease is an impaired fat tolerance. In this study the unsaturated fat oleic acid is made radioactive by adding I_{131} to its double bond, and it has been found that when ingested it behaves similarly to nonradioactive lipid. In this test the patient, after an overnight fast, drinks cream mixed with 5 ml of I_{131} labeled triolein and the blood collected at 3, 5, 7, 9, and 24 hours. The blood is then analyzed for lipid bound I_{131}, and also for the optical density of the plasma, which would be a measure of the lipid present. In a study involving 31 men age 43 to 66 who had suffered a myocardial infarction at least one month prior to the study, and suitable controls, it was found that the optical density, and plasma I_{131} triolein concentration were significantly higher in the patients with Coronary Heart Disease. The differences between the healthy and the diseased were most marked nine hours after the ingestion of the fat. However 13% of the diseased patients had a normal response with respect to the levels of I_{131}, therefore they concluded that the fat tolerance test was not invariably positive in patients with Coronary Heart Disease, and it seemed unlikely that it would be a highly reliable test in revealing preclinical heart disease.[36, 37]. Nevertheless the fat tolerance test with I_{131} distinguished between the healthy and diseased people more effectively than the level of fasting cholesterol or fasting total

esterified fatty acids, and it may be of greater value than these indexes in predicting susceptibility to heart disease.

Familial Hyperlipemia

A disease called familial hyperlipemia was described in 1932 and was diagnosed by the turbidity of the fasting serum and later by an abnormality in the fat tolerance. It is an inborn error of lipid metabolism characterized by elevated levels of serum triglycerides, cholesterol and phospholipids, and is differentiated from familial hypercholesterolemia by the milky serum in the fasting state due to the elevation in the triglycerides.[38]

It has been shown that after the ingestion of I_{131} labeled triolein by patients with this condition excess amounts are retained in the blood stream, and this occurs to a degree in patients with Coronary Heart Disease. The serum level of I_{131} labeled triolein was significantly elevated in the Coronary Heart Disease patients only at the ninth hour afterwards, and it was significantly elevated in the familial hyperlipemic patients at the ninth and twenty-fourth hours. Studies of 24 hour urines revealed that 32% of the labeled I_{131} was excreted in the familial hyperlipemic patients, 45% in the Coronary Heart Disease patients, and 50% in the healthy individuals. These studies suggest that there is a defect in the removal of ingested triglyceride, and also a delay in its excretion both in those affected with familial hyperlipemia

and Coronary Heart Disease: the difference here being maybe only a matter of degree. Serum determinations of triglycerides and cholesterol in familial hyperlipemia and Coronary Heart Disease also reveal similar abnormalities as indicated by the following chart:

Table III

	Triglycerides (milliequivalents/liter)	Cholesterol (milligrams percent)
15 Healthy People	3.4 ± 2.2	222 ± 38
15 Coronary Heart Disease	5.5 ± 2.9	316 ± 74
15 Familial Hyperlipemia	58.5 ± 34	511 ± 58

Familial hyperlipemia is associated with Coronary Heart Disease in 34% and is also associated with diabetes mellitus, exanthomosis, and hepatospleenomegally. A study in Sweden showed that 3% of a thousand college students had familial hyperlipemia.[39] If this incidence is true then the relationship between hyperlipemia and the development of Coronary Heart Disease may be a close one, however it still remains to be proven.

Epidemiology of Coronary Heart Disease in the United States

There have been epidemiological studies in this country and abroad to correlate such factors as blood lipids, daily activity, diet, and socioeconomic conditions to Coronary Heart Disease. Probably the most intensive study is being carried on in Framingham, Mass. During 1948-1950 the National Heart Institute established a field study here to study the extent and development of cardiovascular disease in a cross section of population. The object was to characterize the population which developes a disease and to indicate in what particulars it differs from the segment of the population not subject to the disease.[10] The sample size and age distribution were chosen to provide an adequate group of persons to be observed 20 years or more, thus those studied at the start were aged 30 to 59. Evidence of Coronary Heart Disease was made on the basis of 1) clinical and ECG evidence of myocardial infarction, 2) evidence of myocardial infarct by ECG only, 3) sudden death with or without preexisting evidence of Coronary Heart Disease, 4) angina pectoris, and 5) myocardial fibrosis leading to congestive heart failure. In 1959, 4,469 were examined.[41]

The presence of high blood pressure was strongly associated with the development of new arteriosclerotic heart disease. Hypertension was associated with a 2.6 fold increase in risk of developing arteriosclerotic heart disease in men age 40 to 59, and hyper-

tension increased the risk six times in women of the same age.[42]

With respect to the relationship to weight, they found that an increase in weight after age 25 was associated with an increased risk of Coronary Heart Disease. The United States Life Insurance Companies have shown this same relationship. However this was in contrast with a study of Ancel Keys in which he found only 4.8% of a group of 105 men with Coronary Heart Disease as being overweight. In the Framingham study in evaluating 52 men with arteriosclerotic heart disease, 19% exceeded the relative weight which they calculated as the ratio of the individual's weight to the medium weight for his sex and height group.

The risk factor associated with obesity defined as weight percentage with respect to normal standard weight for a particular age and height is as follows:

Table IV

Risk Factor	Number at Risk	Number developing CHD	Incidence Number/1000/4 yr.
Non-obese	303	13	43
Moderate obesity (15% over)	226	15	66
Markedly obese (25% over)	138	12	87

Consequently this indicates an increased risk with respect to development of Coronary Heart Disease in those people who weigh over that weight designated as normal for their particular age and height, and

the greater the weight, the greater the risk.[43]

In studying the relationship of blood cholesterol to the incidence of arteriosclerotic heart disease in males 45 to 62, the following was found in the four year follow-up:

Table V

Cholesterol mg%	Population at Risk	New Disease	Rate/1000
	898	52	58
260 & above	172	21	122
225 - 259	265	12	45
Below 225	445	18	40

A comparative study of Coronary Heart Disease in Albany, New York, of 1,913 people ages 39 to 55 revealed the following relationship between cholesterol and new cases of arteriosclerotic heart disease:

Table VI

Total Cholesterol	Populatiomn at Risk	New Cases	Rate/1000
Below 200	457	5	11
200 - 274	995	14	14
275	209	13	62

There is a decided difference in the rate per 1,000 of new cases in the two studies among those with high cholesterol levels, however the significant fact is that in both studies the individuals with higher cholesterol levels are apparently a greater risk for the development of Coronary Heart Disease.[44]

The results at the end of six years of study of 5,127 individuals who were initially free of disease revealed 186 new cases of arteriosclerotic heart disease. In men the cholesterol levels tended to be higher for those who subsequently developed arteriosclerotic heart disease in the six years of observation than in the population at risk. The elevation was most marked for men in the youngest age groups and diminished with age. In evaluating the men and woman in the age group 40 to 59 using Chi^2 the following was observed:

Table VII

	Cholesterol Mg %	New ASHD	Pop. st Risk	Incidence/1000 Observed	Expected
Men:	Under 210	16	454	35.2	69.4
	210 -- 244	29	455	63.7	70.8
	Over 245	51	424	120.0	71.8
Women:	Under 210	8	445	18	25
	210 - 244	16	527	30	31
	Over 245	30	689	43	38

The expected rate was calculated by applying age specific incident rates in the Framingham Study Group to the population in the specified category of sex and cholesterol.[45] It is interesting to note that in men with the cholesterol below 210 mg% there was an observed incidence of 35/1000 and expected of 69/1000, and this was significant to the 5% level; and of those with cholesterol over 245 mg% the observed incidence of the new arteriosclerotic heart disease was 120/1000 and the expected incidence was 72/1000 and this was

also statistically significant. Thus those with cholesterol over 245 have more than three times the incidence of arteriosclerotic heart disease as those with cholesterol levels less than 210 mg%. In women of the same age the incidence is 1.6 times greater. No new arteriosclerotic heart disease developed in women less than 40 years of age, and significant elevation of the cholesterol was evident for women aged 40 to 49 who developed arteriosclerotic heart disease, but not for women 50 to 59.

The manifestations of arteriosclerotic heart disease are different in each sex. During six years of the Framingham Study of arteriosclerotic heart disease the incidence rate per 1000 was for males and females as follows:

Table VIII

Age	Males	Females
30 - 44	24.9	1.9
45 - 60	90.6	44.6

The difference in the ratio of arteriosclerotic heart disease in young males as compared to young females is 12 fold, the gap closes after age 45 so that only a two fold difference exists. Angina occurred in 70% of the females affected and this was unassociated with myocardial infarctions, whereas angina occurred 30% of the males affected and was associated with myocardial infarctions. Sudden death occurred in the females in 5% affected with arteriosclerotic heart disease and in 20%

of the males. Of the 88 cases of myocardial infarction occurring in the men 30% died within three weeks. It is also noteworthy that 45% of the initial myocardial infarctions never got hospital-ized, because of these, one-half didn't get a chance because of sudden death, and one-fourth were not hospitalized because it was not clinically recognized, only by ECG. In summary, of the men affected with arteriosclerotic heart disease, 37 of 125 (30%) died of myocardial infarction within three weeks, 7 had only ECG evidence, 24 died of sudden death and of these 62% had no previous history, and 37 had angina. Consequently over one-half the men developing arteriosclerotic heart disease died and one-fifth suddenly, so that there was little opportunity to apply clinical and laboratory studies. Therefore it seems imperative that we find methods to prevent this disease, because except in the female there isn't a good chance to treat the disease after it becomes clinically manifest because of the mortality. Cholesterol deter-minations in these studies seemed to be effective in elucidating the susceptible ones. Although this study didn't reveal that all those with cholesterols over 260 will have a myocardial infarction, or that all those with cholesterols under 260 won't have Coronary Heart Disease, it did reveal that a greater percentage of those with high cholesterol will have Coronary Heart Disease and that this percentage may be reduced by methods used to reduce blood cholesterol.

Epidemiology of Coronary Heart Disease in other Countries

Dr. Ancel Keys has done much work in relating the epidemiological factors of blood cholesterol and dietary fats with the incidence of Coronary Heart Disease in different countries. He feels that many factors are involved in atherosclerosis but that there is no longer any doubt that the concentration of cholesterol and other blood lipids are related to the process. He feels that the cholesterol, phospholipids, beta lipoproteins, are all intimately interrelated and that none by itself affords a safe basis for prediction about the disease process in the individual. As a discriminator between Coronary Heart Disease patients and controls total cholesterol seems to have much the same value as some other measurements and it is technically simpler. Besides, cholesterol is the main intruder in the actual lesions, and it comes from the blood. Repeated dietary surveys on large numbers of persons in whom the cholesterol in the diet failed to disclose a relationship between the cholesterol in the diet and in the serum, but to him this did not mean that the diet was unimportant in regard to the cholesterol levels in the blood. His experiments on men clearly showed that the cholesterol changed in direct relation to a change in the total amount of fat in the diet. Americans in modern times eat a relatively high fat diet, whereas 40 years ago the fat calorie percentage was 30%, now it is 40%. No other country matches

this country in fat consumption.

Studies done by Keys evaluating cholesterol levels with respect to age and diet in different countries have given us much information. Using for normals several thousand clinically healthy men in Minnesota of the urban white collar class, he found an interesting age trend and a considerable variation between individuals at any given age. The mean value for men aged 20 was about 130 mg% and this tended to rise more or less linearly with age until age 50 to 60 years where the means were about 260 mg%; in very old persons low values predominated. This age trend in cholesterol was very similar to the findings on the incidence of marked atherosclerosis at autopsy.

These characteristics of clinically healthy men in America were compared with findings in Italy, England and Spain. A study was carried on in Naples in 1952, where the average of the diet both of the whole population and the particular men studied derived

showed that the Minnesota and Neapolitan trends were not significantly different in youth but around age 30 they began to diverge. In the fifties the Minnesota men averaged 40-50 mg% higher than the Neapolitans. It might be asked, whether this difference was related to relative obesity in the two countries. Actual measurements, however, showed that Italian subjects were just about as fat as our Minnesotans as gauged both by relative body weights and by the measurements of the thickness of subcutaneous fat.

The study in Madrid, Spain, included 105 poor families who were found to be on a diet low in both fats and total calories. Again in comparison with Minnesotans the correspondence in youth and the divergence after the age of 30 was striking with respect to the cholesterol concentration. In their fifties these Madrid men averaged 50 mg% lower than the Minnesotans. Whereas the small wealthy and professional class in Madrid lived on a diet at least as luxurious and as high in fats and calories as in the United States and their cholesterol levels paralleled those values of the Minnesotans.

The study of London males revealed a similar trend with respect to the variance of the serum cholesterol with age; and the diet of the group studied was like that of the Minnesotans. The relationship of serum cholesterol to age in the different groups studied was as follows:

Table IX

Cholesterol given in terms of mg%

Age	Naples	London	Poor Spaniards	Rich Spaniards	Minnesotans
20	135	187	181	202	180
30	216	205	215	217	-
40	231	248	223	243	-
50	229	255	210	264	260

In relating these figures to the incidence and mortality from Coronary Heart Disease, for Spain, they could only say that Coronary Heart Disease was strikingly uncommon in the general popu-

lation as surveyed in the hospitals and public clinics. There were however many cases among the wealthy patients of the practitioners. Unfortunately Spanish vital statistics were either practically nonexistant or relatively unreliable.

The comparison between the males in Minnesota, London, and in Naples with respect to the incidence of Coronary Heart Disease was established by the following chart:

Table X

Deaths of men in 1948 and 1949 in terms of per 1000 of given age ascribed to all circulatory disease and to degenerative heart diseases (myocardial and coronary heart disease.)

Category	All Circulatory Diseases		Degenerative Heart	
(Age)	40 - 44	50 - 54	40 - 44	50 - 54
U.S. Whites	1.66	5.65	1.19	4.44
England & Wales	0.7	2.73	0.27	2.04
Italy	0.63	1.86	0.25	1.02

These statistics revealed a higher incidence of coronary disease in the United States whites; however these figures can only be used to estimate a trend because we know that before the classification was revised in 1949 there was much ambiguity in the classification and also other figures don't reveal this much divergence between Coronary Heart Disease in the United States and England.[46]

In 1956 Keys extended his study to include some clinically healthy Japanese men engaged in sedentary occupations in Japan, Hawaii, and Los Angeles. Of all the large countries with detailed

vital statistics, Japan reports the lowest mortality rate from Coronary Heart Disease. Dr. Paul White and other internists who checked hospitals in Fukuoka, Japan, and in Honolulu, Hawaii, testified that Coronary Heart Disease was fairly common among Japanese in Hawaii but very rare in Japan. However hypertension was common in both regions.[47]

The frequency of severe atherosclerosis in consecutive autopsies on men in Minnesota, Caucasians and Japanese men in Hawaii and Japanese men in Japan , is revealed in the following chart:

Table XI

Age:	30-39	40-49	50-59	60-69
Men in Minnesota	20%	42%	68%	72%
Caucasians in Hawaii	18%	38%	62%	78%
Japanese in Hawaii	5%	8%	30%	34%
Japanese in Japan	2%	4%	8%	10%

Comparing the Japanese in California, it is known that Coronary Heart Disease is their leading cause of death and the representation of the disease in the Japanese Hospital in Los Angeles and in private practice is much the same as for the Caucasians in California.[47]

The serum cholesterol was compared in these same groups of people. The serum cholesterol for 110 Japanese men in Hawaii averaged 76 mg% higher than for their 153 counterparts in Japan, while the serum cholesterol for the 831 Minnesotans was still higher. Another study of Japanese men age 40 to 49 revealed the following relationship to serum cholesterol:[47]

Table XII

45 Japanese men in Los Angeles	205 mg%
35 Japanese men in Hawaii	180 mg%
54 Japanese doctors in Japan	155 mg%
55 Japanese clerks in Japan	118 mg%
57 Japanese miners in Japan	114 mg%
50 Japanese farmers in Japan	112 mg%

Comparing this to their fat intake, fat provided less than 10% of the total calories for the farmers in Japan, and the highest fat intake was that of the physicians in Japan who got an average of 22% of their calories from fats. In Hawaii the Japanese men of this age averaged a little over 30% of their calories from fat, and in Los Angeles the average was almost 40%. The serum cholesterol was linearly related; however this relationship was not dependent upon differences in amount of obesity.

A study of the incidence of coronary atherosclerosis foundiin autopsies of American soldiers killed in Korea was done and compared with a similar study of Japanese men. The series consisted of 300 American men with an average age of 22.1 years. In 77.3% there was some gross evidence of coronary disease which varied from minimal eccentric thickening to complete occlusion of one or more of the main coronary branches. Over 50% of luminal occlusion was found in 20 cases. During a five year period, 1,480 medical examiners cases of all ages in Japanese cities were analyzed and only 14 were coded as coronary deaths. In studies conducted on these Japanese, lesions were found in 65% of those studied, and the plaques were located at the same places as those found in the Americans which

were at places of stress. There were two main differences in the two studies: 1) There were no plaques over 50% luminal narrowing in the young Japanese males 20 to 30 years of age, and 2) The amount of phagocytized lipids in the stroma of the plaques were far less in the Japanese series than in the American series. This implies the possible influence of the plasma lipids and indirectly the fat in the diet.[48]

These studies point to a cultural and economic relationship to Coronary Heart Disease, because the Japanese in Japan comprising the working class adhere more to the diet of their ancestors which does not include a diet high in animal fats consequently their serum cholesterol is low comparitively as is their incidence of Coronary Heart Disease. As the Japanese of Japan become more educated and economically sophisticated and are financially able, they become more atuned to the customs of the world around them and indulge in the delicacies of the Western world which includes in the realm of diet, a diet high in animal fat, and this is reflected in the studies of the Japanese physicians. Then as the Japanese emigrate to Hawaii they become more influenced by Western Culture and dietary customs as indicated by an increase in their dietary animal fat and consequently an increase in blood cholesterol and incidence of Coronary Heart Disease. When these Japanese people emigrate to California they become entirely engulfed by American customs and suffer the penalities of such luxury as shown by their

incidence of Coronary Heart Disease associated with a corresponding increase in serum cholesterol. Thus these studies point more to an environmental relationship of Coronary Heart Disease than a racial relationship.

A study done in Capetown, South Africa, has provided the relationship between the incidence of Coronary Heart Disease, cholesterol, diet and different racial groups at different states of social and economic development.

Table XIII

The relationship of mortality from arteriosclerotic heart disease to cholesterol levels and fat in the diet in different socieconomic groups in Capetown, South Africa:

Socioeconomic Group	Mortality from ASHD per 100,000 ages 55-59	Cholesterol mg%	Diet % Calories from Fat
European	628	242	40
Cape colored	274	195	25
Bantu	Low	168	17

The relationship implied is that the higher the social economic status regardless of race the greater the percent of total calories of diet is composed of animal fat which increases the total cholesterol and thus predisposes to Coronary Heart Disease.[49]

An evaluation of the racial pattern of Coronary Heart Disease reveals that the negro male in the United States of middle age has a similar incidence of Coronary Heart Disease as the white males, however they have a higher prevalence of hypertension, and lower

rates of increased serum cholesterol and obesity. On the other hand, the negro females have higher rates of Coronary Heart Disease than white females, and they have higher rates of hypertension, obesity, and diabetes mellitus, and similar prevalence rates of increased serum cholesterol compared with white females. This study discloses that possibly racial factors are influencial, because the negro people have a similar incidence of Coronary Heart Disease as the white people, but it seems to be more closely related to hypertension which is more prevalent in their race, and less closely related to serum cholesterol. However, this study did not designate whether or not those negroes with an increased serum cholesterol value would be more susceptible to Coronary Heart Disease.[50]

Serum cholesterol changes with age among different people under influences of different diets. Middle class American cholesterol levels tend to rise with each decade of life -- a pattern absent in the Bantu of South Africa, or in the poorer classes of Italy or Spain, but present in the wealthier classes. Economically underdeveloped countries get less than 20% of calories from animal origin whereas the American gets 41%. It is interesting to note that generally in the economically underdeveloped countries malnutrition, infections, parasitic infestations are the killers, whereas in the economically developed countries the degenerative diseases have replaced the epidemic infectious disease and diseases

of undernutrition. Thus, populations subsiding on diets low in percent of calories from fat seem to be immune to Coronary Heart Disease, whereas populations with high percent of fat in the diet may or may not be susceptible to the disease depending upon sex, endocrinology, heredity or possibly type of work.[13]

The population of economically developed countries differ in many respects besides diet: such differences include race and ethnic relations, climate and geography, urbanisation, availability of non-human energy, habitual physical activity, cultural traditions and psychological make-up. It has been found that race and ethnic relations and climate and geopraphy don't play a part directly, but only in-so-far-as they influence the socioeconomic factors of which dietary habits are most important.[43]

In the United States atherosclerosis and its various manifestations rank number one as causes of death, and premature Coronary Heart Disease is occurring with epidemic frequency among middle aged urban and rural men of virtually all socioeconomic, ethnic, and racial strata throughout the country. All exhibit high mean levels of serum lipids and correspondingly similar diet patterns of increased intake of animal foods, saturated fats, cholesterol and refined carbohydrates.[43] Whereas there is a lower incidence of Coronary Heart Disease in primitive tribes of Africa, certain population groups of Italy, Spain and Greenland where fats comprise a smaller proportion of their diet. Orientals who subsist on a

vegetarian diet have a lower incidence of Coronary Heart Disease; however Japanese, Americans, Bantu, Scandinavians and Hawaiians show a straight line relationship between the percent of calories in the diet from fat, levels of blood lipids, and incidence of Coronary Heart Disease.[51]

There is not uniform agreement to this relationship in population studies of diet, blood lipids and incidence of Coronary Heart Disease. One observer points out that the methods used in such studies employed the indirect method of study in the observation of groups, and that from the indirect method, association to the individual could be made, but was not proof of a cause and effect relationship. It has been pointed out that in countries using 30 to 40% calories from fat the mortality varies greatly: for example, in Austria and West Germany there is a death rate of 300/100,000 due to Coronary Heart Disease, whereas in Australia and Canada there is a death rate of 600/100,000.[52] Also the basic data is subject to limitation both as to the components of the diet in which it is almost impossible to determine the fat actually eaten and the actual mortality because of the confusion in classification. Another rebuttal is the fact that the presumed association is not specific for fat in the diet or for disease of the heart. For example, the association with heart disease is stronger when animal protein is substituted for fat and there is a strong negative association for both aniaml protein and fat with mortality from non-

cardiac diseases.[52]

Data of fat consumption, cardiovascualr deaths and population estimates from 12 countries -- Australia, Canada, West Germany, Denmark, Israel, Italy, Japan, New Zealand, Portugal, Sweden, and the United States were made. Scatter diagrams for males for seven age groups by percent of calories derived from fat and death rates per 100,000 from Coronary Heart Disease were plotted and no significant correlations were found. For this reason, they felt there was no rationale for the statement of strong parallelism in different countries between fat consumption and heart disease mortality. These remarks exemplify the fact that the relationship between diet, blood lipids, and incidence of Coronary Heart Disease, is not conclusive and is not accepted by all authorities, however it is significant enough to stimulate further study.[53]

Physical Activity and Coronary Heart Disease

Another relationship was studied by Dr. J.N. Morris of England, who associated physical activity and one form of Coronary Heart Disease which he called ischemic myocardial fibrosis. The report dealt with the relations between physical activity of work and frequency of ischemic myocardial fibrosis in a sample of 3,800 middle aged men dying from causes other than Coronary Heart Disease.

Two broad types of ischemic myocardial fibrosis in the left ventricle and interventricular septum were described. 1) The

large discrete often solitary patches which were the end result of major infarction and associated with complete or near complete occlusion of the main coronary arteries occurring in 90 of the 3,800. 2) The smaller, commonly multiple scars resulted from a more chronic and lesser focal narrowing of the coronary arteries or branches accounting from the remainder of those studied.

The occupations were classified as light, active, or heavy, and the following relationship was found: Ischemic myocardial fibrosis was more common in the light occupations than in the heavy and active ones. Scarring among light workers aged 45 to 60 was as common as in heavy workers 10 to 15 years later. Large healed infarcts were three times more common in the light workers than in the heavy workers overall; four to five times more common in 45 to 60 age groups and two to three times more common in the 60 to 70 age groups. The actual occlusion of a main coronary artery was common in the light workers. The results showed that atheroma of the coronary walls were not related with the physical activity of occupation, occlusion of the vessel had some relationship, and ischemic myocardial fibrosis had a significant relationship.[54]

A study by Dr. Ancel Keys in Sweden of 869 clinically healthy men aged 20 to 59 in the city of Helsinki and in two rural regions relating type of occupation and blood cholesterol showed that in the age range of 40 to 49 the men in occupations demanding heavy physical work had lower cholesterol levels than the man in the lighter

work, but at other ages the cholesterol level appeared to be unrelated to habitual physical exercise.[55]

The study of Morris suggests that the physical activity reduces the myocardial fibrosis and if it occurs in those actively engaged in physical stremuous work then it is manifest by smaller, more numerous areas of fibrosis which are less likely to result in death, at least not in a relatively short period of time. This phenomenon could be due to the formation of anastomotic channels to a greater extent in those people engaged in more vigorous activity.[54]

Dr. A.M. Masters, in reviewing his myocardial infarct cases, found that 40% were workers and laborers although this group made up only 50% of the general population. Store, office, and business occupations accounted for 46% of his cases, yet this group accounted for only 39% of the general population.[56] This is a rough correlation between the physical activity and incidence of Coronary Heart Disease, but it agrees with the more detailed study of Keys and Morris.

On the other hand, Stamler showed that in a study in Chicago of white males from the lowest medium income brackets there was a higher age specific Coronary Heart Disease death rate among the unskilled laborers than males from other occupations of similar age and race.[13] With respect to their diet the United States Agriculture Information Bulletin revealed that low income families in

the United States eat diets as high as high income families in calories, starches, refined sugars, fats and oils, but ate significantly less fruits, vegetables, milk, eggs, meats, poultry, and fish. If one can assume that the male of the lower income families engages in a physically active vocation more frequently than the male of a higher income bracket, then according to Morris their rate of Coronary Heart Disease should be proportionately lower than those in the higher income classes. However the low income families indulge in a high calorie, high fat diet, and this is perhaps more of a factor in promoting the development of Coronary Heart Disease than physical activity is in hindering its development.

A study by Metropolitan Life Insurance Company and was based on mortality experience among different classes of insured lives involving industrial and ordinary policy holders. Industrial policyholders are for the most part members of the urban wage-earning families in lower income brackets. Ordinary policyholders are drawn mainly from the urban middle and well to do classes of the population engaged in professions, business, trade and clerical occupations. Under age 65 the industrial policyholders representing lower socioeconomic groups experienced distinctly higher death rates from arteriosclerotic heart disease than ordinary policyholders. These trends were corroborated by a recent Public Health Service study.[8] Now if we can assume that the industrial policy holders for the most part were engaged in a more strenuous type of

activity than the ordinary policyholders then we can see a possible discrepency in the relationship proposed by Dr. Morris. However the relationship between a decreased incidence of Coronary Heart Disease and habitual physical exercise is important to keep in mind in formulating a possible prophylactic scheme.

Smoking and Behavior Patterns Relating to Coronary Heart Disease

Another important factor which has been considered as being important in the etiology of Coronary Heart Disease is cigarette smoking. In an article summarizing the combined experience of the Albany and Framingham studies concerning the relationship of cigarette smoking and Coronary Heart Disease the following was found:

Table XIV

Smoking History	Number of Men at Risk	Incidence of Myocardial Infarction		Incidence of Deaths from Myocardial Infarction		Incidence of Deaths from All Causes	
		No.	Rate	No.	Rate/1000/yr.	No.	Rate
Non-cigarette Smokers	812	11	2.1	2	0.4	5	9
Cigarette Smokers	1272	66	7.3	23	2.4	52	5.8
All	2084	77	5.4	25	1.8	57	3.9

The men studied were 40 to 59 years of age and free of Coronary Heart Disease at entry into the study. These results point to a possible preventable factor in combating Coronary Heart Disease.[57]

There have been studies relating behavior patterns to incidence

of Coronary Heart Disease. In one such study they compared the behavior pattern characterized by intense ambitions, competitive drive, constant preoccupation with occupational deadlines with behavior pattern with absense of drive, ambition, sense of urgency or desire to compete. Both groups were similar in fat intake, physical activity, age, height and weight; however the former group had clinical Coronary Heart Disease seven times more frequently.[58] The characteristic in the behavior which here is implied as predisposing to Coronary Heart Disease is one which is highly respected in our society and is held as virtuous. Our society tells us to strive hard toward a worthy goal, develope your mind, so that you and others may eat well, and not have to exert yourself physically. However these three virtues are all implied as predisposing to Coronary Heart Disease and consequently, is it a disease created by our society?

Predictive Value of Lipid Determinations in Coronary Heart Disease

The big question which has evolved from these studies is whether or not one can predict with any degree of accuracy by finding an elevated lipid level which individual will develope Coronary Heart Disease? If so, which lipid determination would be the most feasible? This task was undertaken by the joint efforts

of the Technical Groups of the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council and published in 1956. Their purposes were: 1) to obtain further confirmation of the existence of a correlation between an elevated S_f 12-20 fraction of the blood of normal persons and subsequent development of a myocardial infarction, and 2) to compare the total cholesterol and the S_f 12-20 factors as indicators of this disorder. They based their study on the fact that the estimated annual incidence of myocardial infarction in apparently well men age 40 to 59 was 10/1000, consequently they calculated that a base population of 10,000 would yield possibly 100 new events. Their population sources was largely industrial organs but also represented executive, clerical, sales, and labor personal who appeared for their companies annual examination. Four laboratories took part in this study and they were located at the Cleveland Clinic, Donner Lab in San Francisco Harvard in Boston, and at the University of Pittsburg.

The same type of determinations were done at all the labs and were checked for accuracy and reproducibility. The base population was 4,914 and produced 82 new events in three years. The cholesterol measurement of all the labs combined showed a highly significant ability to place the subjects with definite new events above the fiftieth percentile. The cholesterol level was also signigicant in comparing mean values of the measure in group of new events

with the mean value in the base population. Taken as a group the data suggested that the cholesterol was the most effective measure in separating out new events. However during the study the Gofman group at Donner Lab found that the method suggested for analysis of lipoproteins was not accurate enough and devised a new method. However the other three labs had started and did not revise their technique. Gofman had discovered that all four standard lipoprotein classes showed positive and independent association with Coronary Heart Disease. So the combined measurement was termed the atherogenic index and they felt that this was significant for the new events, and they felt that the serum cholesterol was not as significant. However the final decision of the technical group said that the index measurement described in this work had serious disadvantages when compared with cholesterol because of the cost and technical difficulty.[59]

In charts showing the cholesterol and lipoprotein levels of those with definite myocardial infarcts, it was apparent that none of these measurements led to any clear separation of new events at high levels and none regularly placed individuals in the upper one-half of the distribution. The way they evaluated that lipid levels were of no use in predicting individuals who would get the disease was by the S-shaped curves which indicated the position of those who acquired the disease with reference to the cumulative distribution of the appropriate base population. Each definite

event was located on its appropriate distribution curve according to the lipid measurement it showed. If the elevation of the lipid measurement did permit prediction of the development of clinically manifest arteriosclerotic heart disease the subjects experiencing the definite new events should have had lipid levels in the upper part of the distribution curve of the base population. In this study it was apparent that none of the measures lead to clear separation of definite new events at the high levels and none regularly placed the individual in the upper one-half of the distribution. In summary the elevation of cholesterol and lipoproteins in serum was of no clinical use in predicting those individuals who would develope a myocardial infarct. They thought however that the level of the lipoprotein and cholesterol in the serum of groups of men who developed Coronary Heart Disease may have a useful application in the epidemiological studies of heart disease.[59]

Detection of Cardiovascular Disease Without Using Lipid Determinations

Utilizing other methods than the analysis of blood lipids to find those in the general population who actually have cardiovascular disease a study was done in Newton, Mass., from 1949 to 1952, with the combined cooperation of the local, state and national health departments. Eight thousand people were screened who were not under care for heart disease, and those referred for further

evaluation were those with a history of angina, heart attack, exertion dyspnea, paroxysmal nocturnal dyspnea, orthopnea, rheumatic fever, chorea or heart murmur. They were referred for further evaluation if physical examination revealed blood pressure over 160/96·, or evidence of a heart murmur meaning systolic grade 3/6 at least or any diastolic murmur. Of those studied, 17% had suspected cardiovascular disease, and in 45% of the original 17% cardiovascular disease was confirmed. In other words 3.7% of the population studied had difinite cardiovascular disease which was unknown to them.[60] The etiology of the 3.7% was:

Table XV

	Number of Cases
Rheumatic Heart Disease	49
Hypertension	96
Hypertensive Heart Disease	66
Arteriosclerotic Heart Disease	36
Others	18

However statistics published by the American Heart Association for 1955 reveal the following death rate per 100,000 in the United States:[61]

Table XVI

Disease	Rate/100,000
A. Arteriosclerosis	266.8
1. Arteriosclerotic Heart Disease including coronary	247.0
2. General Arteriosclerosis	19.8
B. Hypertension and Arteriosclerosis	145.9
1. Cerebral Vascular Lesion	106.0
2. Non-rheumatic endocarditis and myocardial degeneration	39.0
C. Hypertension	
D. Rheumatic Heart Disease	

Consequently the type of screening test as described previously was effective in picking up cardiovascular disease, but it did a rather poor job of detecting the one disease, that of arteriosclerotic heart disease, which accounts for more deaths than all of the other conditions listed do altogether.

Method for Detecting Coronary Prone Individuals

The mortality from the first attack of Coronary Heart Disease is high, approximately 35% and 20 to 40% recovering die within the next five years; therefore it is imperative that we detect those susceptible to Coronary Heart Disease before it is clinically manifest.[43]

What are the risk factors which may be associated with Coronary Heart Disease, so that they may be recognized and steps can be taken to circumscribe the process? 1) Hypercholesterolemia --

over 260 mg% is associated with a 3-6 fold increase in risk. 2) Hypertension (diastolic over 95) is also associated with a 3-6 fold increase in risk. 3) Obesity, long history of cigarette smoking, diabetes mellitus, hypothyroidism, and kidney damage are associated with a significant increase in risk. Habitual physical inactivity and hypomaniac personality patterns also are implied.[43] 4) Family history of Coronary Heart Disease is associated with an increased risk because there is a positive history of Coronary Heart Disease in parents, brothers, or sisters in 7% of the males affected and 10% of the females affected.[4] 5) ECG is useful because non-specific T-wave change abnormalities are associated with an increased coronary proneness.[43]

Thus the coronary prone individuals may be detected by a good history and physical examination dwelling on the points listed above, and by determining serum cholesterol, glucose, blood pressure, weight and ECG. It is becoming increasingly evident that coronary proneness is amenable to treatment. 1) Hypercholesterolemia and obesity may be treated by nutritional means. 2) Hypertension and diabetes mellitus may be treated by nutritional and pharmacological means. 3) Heavy cigarette smoking and physical inactivity may be countered by changing living habits.[43]

For example former cigarette smokers who have quit experience lower coronary disease than those who persist. Modern methods of treating hypertension have lowered this predisposing factor, and

persons who reduce and stay reduced are restored to standard risk. Controlled diabetes mellitus experience lower vascular complications, and low fat diets have lowered recurrence and mortality rates in persons surviving previous myocardial infarctions.[43]

Diet and Coronary Heart Disease

One of the principle factors related to an increased blood lipid level is the diet, and specifically the percentage of the total calories derived from fat, and the type of fat. This relationship of the diet of man to the diseases of man is an interesting one that takes us back into history. Historically man has been on earth about 500,000 years, and homosapiens have been on earth 25,000 years, and up until 25,000 years ago he was exclusively a food gatherer -- and knew nothing of cereals, bread, dairy foods, or edible oils; now man is a food producer and processor. At that time it was impossible for primitive man to ingest 40% of calories in the form of lipids. About 8,000 years ago man went from a food gatherer to a food producer and became a farmer and herder, and thus creating preconditions for the present civilization and the kind of diet we Americans have. Upper classes of ancient Egypt consumed a diet very similar to ours and their mummies come down to us with bits of aorta presevered revealing existence of atherosclerosis. At that time the urban and rural masses existed on a beer and bread staple diet -- a similar situation has pre-

vailed for most of humanity right down to and including our own day. The difference between the so-called economically developed countries such as the United States, Britain, and Sweden and the countries such as Spain, Japan, and Africa, is that the majority of the population in economically developed countries have access to the high calorie, high fat diet which is shared only by the upper classes in the other countries where the majority of the populace subsides on the same diet they have for centuries because of existing poor states of economy or cultural reasons.[13]

The relationship between diet and incidence of atherosclerosis became evident after the British blockage of Germany during World War I, at which time it was noted by German pathologists and clinicians that the incidence of deaths and sickness from coronary and cerebral vascular atherosclerosis fell. Then the incidence rose again in the post-war era. During World War II the Scandinavian government reported that fats in the population was reduced because of the scarity of dietary fats, and consequently death and sickness decreased as a result of atherosclerosis.[62]

A descrepancy in this type of thinking was pointed out by the Department of Ministry of Health of Great Britain in 1954 when they showed that the fat intake and deaths from arteriosclerotic heart disease showed post-war increases whereas the pre-war fat consumption was also increased but the atherosclerotic deaths were half the number as compared to 1954. Consequently one must take

the relationship between diet and Coronary Heart Disease as indicating a trend and not an exact relationship.[53]

Cholesterol Lowering Effect of Low Fat Diets

It has not been proven that lowering cholesterol or any of the blood lipids will prevent either the occurance or end results of atherosclerosis exclusively, however there are many reasons for believing that there is some connection between cholesterol metabolism and atherosclerosis and while awaiting for the elucidation to be revealed conclusively it seems justifiable to apply certain dietary procedures. However because of the biological fluctuation of cholesterol, some conservative sources say one must remember in evaluating the effect of diet that to be of significance a cholesterol level checked one time after therapy must decrease 100 mg% or there must be a lesser decrease of 60 mg% which is consistently maintained.[63]

It is known that by decreasing dietary fat which decreases serum cholesterol coronary atheroma will disappear in experimental rabbits and chickens. This may not apply directly to man however cutaneous xanthomata disappear on low fat diets in man. It has been found that reduction of the total calories due to fat in man can produce statistically significant changes in the blood cholesterol and such a response takes place in about two weeks. For example in men hospitalized because of mental disease from ages

thirty to fifty with no cardiovascular disease, normal cholesterol levels and diets normally consisting of between 35 and 40% fats, a diet was given in which the calories were only 20 to 24% fat and the cholesterol was decreased an average of 17 to 25 mg%.[9] However a less optimistic study in Scotland of twelve hypercholesterolemia men with Coronary Heart Disease being treated with a 1200 calorie diet with 15% fat over a four year period resulted in only a 15% reduction of cholesterol.

Cholesterol Lowering Effect of Polyunsaturated Fatty Acids

Besides lowering the percent of fat in the diet, other investigators have had results by substituting polyunsaturated fats for saturated fats and maintaining the same percent of calories from fat. Seventy-nine men of normal weight, aged 50 to 59, with an average cholesterol of 251 mg% were placed on a diet of 2000-2700 calories with fat producing 35% of total calories, and of this polyunsaturated fats comprised 33% of the fat calories. One and one-half ounces of corn, oil, fish, grain and vegetables per day provided the unsaturated fats. The average cholesterol was 251mg% before the change in diet and decreased to 222 mg% after six months of the modified diet.[64] In another study of 300 inpatients averaging age 60 in a state institution a dietary regimen employing a non-hydrogenated corn oil margarine for other solid fats was carried

out. The total fat was approximately the same in the control and test diets, however the big change was in linoleic acid.

Table XVII

	Control Diet	Test Diet
Total Fat	828 gms	700 gms
Calories as Fat	48%	43%
Linoleic Acid	60 gms	153 gms

As a result of this the cholesterol dropped 23% in 5 months from an average of 250 mg% to 193 mg%.[65]

These studies leave some things to be desired. What is the normal percent of unsaturated fats in the diet? Is such an effect manifest in the younger age groups? Can such a diet be given effectively in groups not institutionalized? A study recently done in Cleveland by Doctors I.H. Page and H.B. Brown answer these queries. Their experiment involved medical students and their wives from Western Reserve University, and included 25 males and 14 females in the test group, and 30 males and 19 females in the control group.[18] Polyunsaturated fats were substituted for saturated fats isocalorically. The diet used was felt to be feasible and acceptible to those involved, however it did include some special commercially produced products. The diet consisted of 1) foods which could be purchased in regular markets and contained little fat, such as bread, cereals, fruits, vegetables, condiments, nuts, poultry, and fish, 2) foods not allowed were bacon, rib roast, duck, spare ribs,

tongue, and olive oil, 3) foods prepared commercially were meats deleted of saturated fats and other foods that were filled with polyunsaturated oils replacing saturated fats such as milk, cottage cheese, ice cream, margarine, prepared cakes, cookies and pies. With this diet fats still provided 40% of total calories.

Comparing quantitatively the saturated and unsaturated fats in the normal and experimental diets the following was found:

Table XVIII

	Grams Fat	Grams Sat. Fat	Grams Unsat. Fat
Normal	129	51	63 (49% of total)
Experimental	118	32	86 (73% of total)

Other figures list the average American diet as consisting of 85% saturated fatty acids and 15% unsaturated fatty acids. The 39 subjects on the experimental diet dropped from average baseline concentration of 205 mg% to 176 mg% and maintained it at that level for ten months, whereas in the control group there was no change. The hypocholesterolemic effect was noted in two weeks. In only one individual was there a failure of response, and during exam week there was no significant response to stress. The mean change in the serum cholesterol was 14 mg% as compared to the control group which they considered significant.

Another study revealed that on a test diet giving 42% of calories as fat and of this 33% was modified vegetable oil, four physicians with previous cholesterols averaging 250 mg% maintained this diet

for twenty-one days. This resulted in a drop in the cholesterol of 40 to 80 mg%, while the lipoprotein and triglyceride remained normal. Then when these physicians resumed their normal diets their cholesterol rose to 250 mg% again.[66] The mechanism of actiam of the unsaturated fatty acids is not known, but they are thought to increase the excretion of sterols and bile acids. They also may act the intestinal flora changing the structure of fedal sterols and bile acids thus modifying their absorption.

Effect of Dietary Cholesterol on Blood Cholesterol

Can the cholesterol be depressed by varying the dietary intake of cholesterol? Original studies indicated that this was not the case. For example, a study was done before 1950 by Doctors M.M. Gertler, S.M. Garn, and P.D. White on the dietary and serum cholesterol of 97 men who had experienced Coronary Heart Disease before age 40 and they used 146 healthy men as controls. The average amount of cholesterol ingested per week in the healthy group was 3.88 ± 1.46 grams and in the coronary group 3.30 ± 1.41 grams. Despite this significantly lower cholesterol intake, the serum cholesterol levels in the Coronary Heart Disease patients were significantly higher. The relationship between the amount of ingested cholesterol and the amount of cholesterol in the serum was accomplished by determining the co-efficients of correlation.

Of the coefficients of correlation ± 0.5 was moderate, ± 0.2 low, and below ± 0.1 not significant. In this case the coefficients of correlation between serum cholesterol and the ingested cholesterol were +0.05 ±0.11 for the controls and +0.09 ±0.08 for the Coronary Heart patients. This indicates no relation between the amount of cholesterol ingested and the level of serum cholesterol.[67] However recently it has been shown that cholesterol in the diet can influence the serum cholesterol. For example the additions of crystalline cholesterol-3 grams per day for eight weeks increased the cholesterol in six patients 56 mg% in one study and in another study three men previously receiving a general diet were given a cholesterol free diet and had a decrease of their cholesterol of 61 mg%.[68]

Triglyceride Lowering Effect of Low Carbohydrate Diet

These studies have shown the effectiveness in lowering the serum cholesterol by low fat diets, low cholesterol diets, and diets whose fats consisted mostly of unsaturated fatty acids; however it has been shown that elevated lipoproteins are associated with an increased incidence of Coronary Heart Disease, and this elevation is dependent upon several of the beta lipoprotein fractions and is correlated by the atherogenic index. The atherogenic index may be elevated by an independent elevation of either S_f 0-12 or S_f 12-400

or their elevation together. The point is that the S_f 0-12 is composed of mostly cholesterol and is thus influenced by those factors influencing serum cholesterol, whereas the S_f 12-400 is composed of mostly triglycerides and is thus influenced by an increase in the intake of carbohydrates.

Dr. Gofman feels that there is an increased risk of future myocardial infarction associated with an elevation of the beta lipoproteins S_f 0-12, 12-20, and 20-400 and that this elevation may precede coronary artery disease by at least several years. He revealed that by feeding patients on high animal fat diets for 11 weeks, with also an increase in regular fat, the result was a significant elevation S_f 0-12, and no consistent trend or significant difference in mean levels of the S_f 20-400. Vegetable oils will lower the S_f 0-12, probably because the animal fat is not present. Conversely an increase in the carbohydrate in the diet per day from 220 grams to 385 grams will increase the S_f 20-400 and low carbohydrate intake will lower this. Combining these two it can be seen that caloric restriction with lowering of both the animal fat and the carbohydrate would probably be the most logical dietary regimen.[69]

Dr. Gofman also stated that he felt there was no valid evidence that any protective factor is present in vegetable oils which will lower the S_f 0-12, 12-20. He felt that the effect was due to the reciprocal effect on the carbohydrates and thus also on the S_f 20-400 fraction, because when the diet was high in vegetable

oils, a large percentage of the calories came from vegetable oils thus reducing the amount of calories coming from carbohydrates, and thus reducing the S_f 20-400 fraction. He also felt that the serum cholesterol can be dangerously misleading, because when the cholesterol is decreased the S_f 0-12 is decreased, the S_f 20-400 may be increased and therefore increasing the chance for coronary artery disease.[69]

Analyzing specifically the effect of diet upon the triglyceride levels, it has already been established that an increase in the dietary carbohydrate intake results in an increase in the serum triglyceride level and thus in the S_f 20-400 fraction of the beta lipoproteins. In studies in which people were habituated to a low fat (15%)-low calorie diet, then consuming a high fat (40%) and high caloried diet rich in saturated fatty acids, the serum triglyceride level rose significantly; also in many on the low fat diets the serum triglyceride level rose. Therefore the serum triglyceride level may be elevated by several dietary factors.[70] However recently studies have shown the diets low in fat 4 to 10% of total calories, and high in carbohydrates, 75-85% of the total calories, do lower the cholesterol, and elevate the triglycerides, but this elevation of the triglycerides is transient. In any case it has been shown that diets in which unsaturated fatty acids comprise 10-40% of the total calories, the cholesterol is significantly lowered, as before, however the triglycerides remain the same with-

out elevating. Therefore hypertriglyceridemia does not occur with diets made-up to yield moderate intake of calories, carbohydrates, and total fats, with the percent of saturated fats reduced and unsaturated fats increased.[71]

Dietary Treatment of Those Afflicted with Coronary Heart Disease

Is it worthwhile to treat those who have already suffered from Coronary Heart Disease with diet? A study by Dr. L.M. Morrison in California on 100 patients with Coronary Heart Disease revealed its possible significance. The 100 patients had proven cases of myocardial infarctions and were uncomplicated by hypertension, diabetes mellitus, nephrosis, hypothyroidism or xanthomatosis. He split the patients evenly into two groups: fifty were treated with a low fat diet consisting of 25 grams fat which included 50 to 70 mgs of cholesterol, and the other group (control group) was given a regular fat diet which consisted of from 8-160 grams of fat of which 200-1800 mgs were cholesterol. The average age for the groups was 70 for the control group and 68 for the experimental group with a range of 40 to 78. An appreciable number on the low fat diet required one to two years before a fall in the serum cholesterol was manifest. After 8 years the average weight loss the patients on low fat diets was 21 pounds for the males and 17 pounds for the females. The total serum cholesterol fell during that time

from an average of 312 mg% to 220 mg% and the triglycerides fell from an average of 236 mg% to 120 mg%.[62] After this length of time 76% of the controls had died of Coronary Disease as compared with 44% of those on the low fat diet. After twelve years all the controls had died, and of those on the low fat diet 38% were alive.[72] These results might point out the benefit which may be realized by treating with an appropriate diet those who have already been afflicted with Coronary Heart Disease.

However Dr. R. Gorlin of Boston recently stated that there was no evidence available despite favorable effects of diet on certain measurable components of lipid pattern that morbidity and mortality will be favorably affected by diet in those who have suffered from Coronary Heart Disease. If this method is effective it would be more through changes in the propensity to clotting than to changes in the arterial wall atheroma. However he did consider diet important in overweight patients, and in young patients with Coronary Heart Disease with hyperlipemia.[73]

Dietary Treatment of Coronary Prone Individual

What is the effectiveness of treating the coronary prone individual? Such a study was undertaken and entitled the Coronary Prevention Evaluation Program. The Heart Disease Control Program of the Chicago Board of Health in May, 1958, launched a pilot research study on the ability to achieve primary prevention of clinical

Coronary Heart Disease in high risk men ages 40 to 59. The participants were free of disease at the onset, and were a high risk based upon 1) hypercholesterolemia determined by three weekly serum cholesterol levels over 260 mg%, hypertension with a diastolic over 95, obesity meaning a weight 15% over the desirable weight; any two or all three of these abnormalities; 2) hypercholesterolemia over 325 mg% as a single abnormality, or 3) a fixed non-specific ST-T changes.[43]

The diet recommended for the high risk patients consisted of 1700 calories, with 30% fats, low in saturated fats less than 20 grams per day rather than the normal 45 grams or more per day, low in cholesterol, 300 mg. or less, and moderate in polyunsaturated fatty acids.

Table XIX

Overall changes in dietary nutrient intake of 99 participants in coronary prevention evaluation program were as follows:

	Control	Treatment
Total calories	2465 ± 692	1668 ± 334
Carbohydrates (grams)	230 ± 73	192 ± 49
Protein (grams)	106 ± 31	95 ± 17
Fat (grams)	119 ± 42	56 ± 15
Saturated fatty acids (grams)	48 ± 19	19 ± 5
Unsaturated fatty acids (grams)	66 ± 23	34 ± 9
Polyunsaturated fatty acids (grams)	16 ± 7	12 ± 4
Cholesterol (mg)	627 ± 219	307 ± 93
% of calories from carbohydrates	37 ± 7	46 ± 6
% of calories from proteins	17 ± 4	23 ± 3
% of calories from fat	43 ± 3	30 ± 5
% of calories from Sat. fatty acids	17 ± 3	10 ± 2
% of calories from Unsat. fatty acids	24 ± 3	18 ± 3
% of calories from Polyunsat. fatty acids	6 ± 2	7 ± 2

Table XX

Corresponding changes in serum cholesterol, weight, and blood pressure in 99 participants in the Coronary Prevention Evaluation Program were as follows:[43]

	Control	Treatment
Serum cholesterol	271	231
Weight	196	182
Observed/desired weight	1.269	1.179
Blood pressure	134/88	127/82

This shows the effectiveness of the prescribed diet on the risk factors.

The relationship between the control serum cholesterol and the fall in the serum cholesterol of the 99 participants on the prescribed diet was as follows:

Table XXI

Group based on control serum cholesterol level	Number of Men	Control mg %	Treatment mg %	Decrease mg %	Decrease %
Less than 200 mg%	12	180.7	178.8	1.9	1.1
200 - 224 mg%	9	216.2	197.9	18.3	8.5
225 - 259 mg%	17	244.1	219.6	24.5	10.0
260 - 299 mg%	35	279.2	241.5	37.7	13.5
300 mg% and over	26	340.2	262.4	77.8	22.9
All	99	271.5	231.7	39.8	14.7

This study reveals that the greater the elevation of the serum cholesterol initially the greater the response to the dietary regimen.[43]

In this partioular study the results have not been evaluated yet as to the effectiveness of treating coronary prone individuals with respect to lowering the incidence of Coronary Heart Disease, but the outlook is optimistic.

Effect of Diet on Familial Disorders

Are diets low in fat or unsaturated fatty acids helpful in decreasing the serum cholesterol in familial hypercholesterolemia? In studies evaluating this situation the blood cholesterol seems to be unrelated to the absoluted amounts of carbohydrate, fat, protein, or cholesterol in the diet, and those who were put on low fat high unsaturated fatty acid diets did not respond with a decrease of serum cholesterol below 350 mg% and some actually increased.[74, 75]

In familial hyperlipemia restriction of dietary fat was effective, and in those cases with abnormal fat tolerance and post-prandial hyperlipemia, heparin was effective in clearing the serum of the triglycerides present.[37] However in familial hyperlipemia the use of heparin was occasionally associated with abdominal pain, and increase in the size of the liver and spleen due to the rapid deposition of large quantities of fat in these areas; consequently the use of heparin in these cases must be used causiously. Another limiting factor to the use of heparin is that it must be given parenterally and it is expensive.[76] The most effective treatment in those with abnormal fat tolerance and post-prandial hyperlipemia was spaced fat feedings, limiting fat intake to one meal per day and allowing 24 hours to return to the fasting levels.

Proposed Dietary Regimens

Just what comprises a practical diet for lowering total fats and increasing unsaturated fatty acids? A low fat diet consists of no dairy products except skimmed milk, one egg or 3/4 ounce of cheese, lean meat, fowl or fish, fruits, vegetables and non-fat foods unlimited all in terms of per day, and this provides about 20 to 30 grams of fat per day. This diet reduces the saturated fats which are included in the following foods: butter, whole milk, cream, cheese, egg yolks, fat of meat, coconut oil, chocolate, and most shortenings and margarines.[77]

The effective diets increasing the unsaturated fatty acids supply between 70 and 80% of the calories from fats as unsaturated fatty acids. However these unsaturated fatty acids have little effect when taken in addition to the usual amount of saturated fat as a type of tonic. Also the polyunsaturated fatty acids such as linoleic, linolenic, and arachindonic acids with two, three, and four double bonds respectively are much more effective than the monounsaturated fatty acids such as oleic acid. A source of saturated fatty acids and a source of unsaturated fatty acids are compared revealing the percent of fatty acids in each:[78]

Table XXII

	Saturated Fatty Acids	Mono-unsaturated	Poly-unsaturated
Butter	55%	33%	4%
Vegetable oils like corn oil	10 - 20%	25%	55%

To provide 70 to 80% of the calories from fats as unsaturated fatty acids, first sources of saturated fat must be eliminated as suggested by the low fat diet given above. Secondly sources of polyunsaturated fatty acids must be substituted. These can be provided by vegetable oils of which cottonseed oil are the most practical in this country, however corn and peanut oil are also effective, and polyunsaturated fatty acids are also provided by fish.[79] Consequently by omitting all dairy products except skimmed milk, omitting all meat, and allowing fish, vegetables, fruits, and vegetable oils such as those mentioned in unlimited proportions an adequate unsaturated fat diet is provided.

However some practical problems arise such as providing for the shortenings with which many of our meals are prepared and which at the present time contain a high percentage of saturated fats. As we have seen in the study in Cleveland by Doctors Brown and Page such items can be prepared commercially which contain high percentages of polyunsaturated fatty acids, and these preparations can be used for making spread for breads, shortenings, and can be made to emulsify in a blender with nonfat milk solids to yield reconstituted milk, cream or ice cream. The principle disadvantage is that the usual commercial foods are not necessarily prepared with vegetable oils and hence more home cooking is necessary. Unfortunately the greatest danger in this proposal to a logical development of an effective food pattern are premature claims for virtues without

evidence to back it up and the rush by commercial enterprises to capture the market with the preparation of still unproved value.[66]

Since there has been some evidence that cholesterol in the diet influences the serum cholesterol it might be wise to see what foods contain it in sufficient quantities and those which do not. A study done analyzing the cholesterol content of food samples purchased in open markets resulted in the following:[80]

Table XXIII

	Fatty Acids %	Total Cholesterol % Moist Weight
Beef round (medium fat)	4.6	.125
Pork spare ribs	19.5	.105
Liver beef	3.7	.32
Brain	10.9	2.36
American cheese	28.2	.16
Butter	68.0	.28
Egg yolk (dried)	63.8	3.9
Egg yolk (fresh)	33.1	2.0

This study revealed that of the common foods, egg yolk and brain are the only foods shown to contain more than 1% of cholesterol. The average American diet includes only 400 to 500 mg of cholesterol per day and the body synthesizes twice this amount per day.[81] Cholesterol comprises only a minor constituent of the daily dietary intake, and it is not a major constituent of the common foods compared with the percentage of fatty acids. Therefore the low fat diets cutting down on the saturated fatty acids would be sufficient also to reduce any excess cholesterol in the diet.

Consequently in dietary management the most logical and practical solution seems to be use of a modified polyunsaturated fat diet combined with a diet low in total fats and cholesterol. These changes are effected by emphasizing ingestion of moderate quantities of lean meat such as round steak and veal; poultry, such as game, chicken, turkey; fish and other sea food; skim milk, cottage cheese, whole grain foods, flour products, fruits, vegetables, and vegetable oils. Fat cuts of meat are de-emphasized as are table spreads and solid cooking fats such as butter, margarine, lard, hydrogenated solid fats, bacon and salt pork. Also de-emphasized are chocolate, alcoholic and carbonated beverages, cheese, cream, ice cream, whipped cream, egg yolks, and rich foods such as pastries, pies, cookies, and cakes.[43]

If such a diet were proven to be effective in the prevention of Coronary Heart Disease, the limitation of dairy products would have quite an impact on the dairy industry. As a result of this the National Dairy Council has launched an active campaign to defend their milk products. They state that milk fat from all dairy foods contribute only one-tenth of all calories and only one-fourth of the fat in the diet. They also state that our per capita consumption of milk-fat has remained constant since 1920, while the consumption of other fats has increased. Their biggest argument is based upon the high protein content in milk, which according to some theories is though to be significant because when the phos-

pholipids and or protein levels are diminished the cholesterol carrying vehicle is not adequate to transport the cholesterol and thus the cholesterol is available to enter into the pathogenic process of atherosclerosis. Therefore they contend that the high protein content of milk products more than compensates for the high saturated fat content.[82]

The position of the Council on Foods and Nutrition of the American Medical Association with respect to diet and Coronary Heart Disease as of Dec. 29, 1962, is as follows: "The Council believes that properly instituted diet therapy can significantly and safely alter the serum cholesterol and beta lipoprotein concentrations of most hypercholesteremic human subjects. The Council recommends that when this diet therapy is carried out it should be under the supervision of the physician with adequate follow-up procedures, including laboratory studies. The Council recognizes the importance of epidemiological studies which have shown an association between low serum cholesterol values and low mortality rates for arteriolosclerotic heart disease, although it believes that a causative relationship has not yet been proven." The Council supports and encourages investigations of American population groups to test the effect of properly supervised diet therapy as means of prevention of coronary disease. Finally, the Council believes that, despite the promise of the diet in therapy, there is not sufficient information available at the present time to warrant a change in

the American diet aimed at preventing heart disease in the general population."[83]

Drug Therapy

In the attempt to combat Coronary Heart Disease and working under the assumption that decreased blood cholesterol would be desirable, many chemical agents have been devised to lower the blood cholesterol. Triparanol (Mer 29) was developed specifically to block the endogenous synthesis of cholesterol, and it does this effectively by blocking the last step in the formation of cholesterol allowing the accumulation of the metabolic product called desmosterol. This effectively lowers the blood cholesterol in 80% of those tested, however desmosterol accumulates and may be just as atherogenic as cholesterol. Also there are other side effects such as producing postmenopausal bleeding, increasing the SGOT, producing a positive cephalin floculation test, dermatitis, loss of libido, 50 to 75% decrease in the corticosteroids, and loss of hair. Consequently this drug was removed from the market.[84]

Another agent sitosterol, a plant sterol, when given in doses of five grams, three times per day, may lower the cholesterol 10 to 15% by blocking the intestinal absorption of cholesterol by competitive inhibition, or by forming with cholesterol a crystal which is insoluble and not absorbed; however this has not been accepted.[85, 86]

Nicotinic acid in doses of 3 to 6 grams per day reduces the serum cholesterol by some unknown mechanism; however it may produce such side effects as flushing, pruritus, dry skin, hyperpigmentation, anorexia, hepatic functional impairment with jaundice, a diabetic glucose tolerance curve, and angina.[89] Neomycin in dosages of 0.5 to 5 grams per day may reduce the serum cholesterol by altering the intestinal flora.[84, 88]

It has been noted that serum cholesterol is elevated in hypothyroidism and depressed in hyperthyroidism, and it is also known that thyroxin especially the dextrorotary isomer increases the synthesis and excretion of cholesterol. What has been sought is an isomer of thyroxine that exerts a hypocholesterolimic response without producing cardiac or calorgenic effects.[89] In studies utilizing 4 to 8 mg of sodium dextrothyroxine in patients with Coronary Heart Disease and hypercholesterolemia over periods of 5 months to one year, the serum cholesterol has decreased approximately 32%.[90] However this form of therapy has not been generally accepted. Triparanol, and Nicotinic acid lower the serum cholesterol, but do not reduce the triglyceride concentration or improve the fat tolerance in contrast to d-thyroxine which does.[91]

Another drug, estrogen which is thought to protect the female from Coronary Heart Disease during the premenopausal years has been viewed as being helpful in preventing Coronary Heart Disease. Patients who had died of carcinoma of the prostate and were treated

with estrogen, and those not treated with estrogen were autopsied and the degree of atherosclerosis was evaluated. Those treated with estrogen had evidence of less atherosclerosis.[92] Again this drug and all of the drugs discussed have not been accepted as being of value in the preventive treatment of Coronary Heart Disease or in treating those who have suffered from Coronary Heart Disease, probably because of the skepticism concerning the significance of an elevated blood cholesterol in contributing to Coronary Heart Disease.

Summary

Coronary Heart Disease with its chief clinical manifestation of myocardial infarction, is a primary cause of death in the United States accounting from approximately 30% of all deaths, and is striking down productive men between the ages of 40 and 60 in frightening numbers. This disease which was first described clinically in 1912 has increased rapidly, almost in epidemic proportions since that time. While studying the pathological entity responsible for this disease, atherosclerosis, many years before it was associated with the clinical picture, it was found that these atherosclerotic lesions had an abnormally large amount of cholesterol. Consequently when this disease gained prominence in the early part of this century, high serum cholesterol levels were associated with Coronary Heart Disease. However since this relationship was not constant in all individuals other correlations were sought; and with the development and refinement of chemical techniques and analysis, correlation was made with levels of beta lipoproteins in the blood, and with the development of the ultracentrifuge, different fractions of the beta lipoproteins were more significantly correlated. By analyzing these different fractions chemically it was found that triglycerides were abnormally elevated in those people with Coronary Heart Disease. By studying those people with rare familial hyperlipemias it was found that there was an abnormal tolerance to fat which was also found in

people suffering with Coronary Heart Disease. Many other correlations were made, such as relating Coronary Heart Disease to body build, behavior pattern, and physical activity. An interesting series of investigations involving different populations related a decrease in the incidence of Coronary Heart Disease with a decrease in blood lipids resulting presumably from a decrease of the percent of total calories from fat consumed by the population involved. Similar studies related hypertension, obesity, cigarette smoking, diabetes mellitus, hypothyroidism, kidney disease to an increased incidence of Coronary Heart Disease. It has been advocated that high risk patients can be detected by evaluating their serum cholesterol, blood pressure, weight, family history, and ECG. It has also been shown that diets high in saturated fats, with the fats comprising about 40% of the total calories is associated with an increase in blood lipids and increase in incidence of Coronary Heart Disease. Consequently diets have been recommended for the high risk patients which advocate a moderation of total calories with fat comprised of polyunsaturated fatty acids, and decreasing the amount of dietary cholesterol. This type of diet has proven to be effective, however it is not recommended by the AMA Council on Foods and Nutrition for the general population. Specific drugs have been tried which lower the serum cholesterol, however they have not been generally accepted.

CONCLUSION

I. Thirty percent of all the deaths in the United States are due to Coronary Heart Disease. This disease was rare before World War I, being only clinically described by Dr. J. B. Herrick in 1912, and now is our leading cause of death, causing 270 deaths per 100,000 population.

II. Those with Coronary Heart Disease under age 50 have significant elevation of the serum cholesterol, usually over 260 mg%. The triglyceride level is elevated over 5.5 milliequivalents per liter, apparently more constantly than the serum cholesterol in those with Coronary Heart Disease, and is consistently elevated in those with Coronary Heart Disease over age 50. Those in the normal population with triglyceride levels over the normal level may be the ones most likely to develope Coronary Heart Disease in the future. The triglyceride determination is technically more difficult than the cholesterol determination and consequently is not used as often. The beta lipoprotein and phospholipid determinations have been shown to be elevated significantly in Coronary Heart Disease but they are technically difficult and expensive and therefore not practical. However, the fat tolerance test utilizing I_{131} triolein may prove to be a useful screening procedure in detecting individuals susceptible to Coronary Heart Disease.

III. Epidemiological studies in the United States have revealed an increased incidence in Coronary Heart Disease in those with hypertension and in those who are overweight. People with serum cholesterol over 260 mg% have three times the incidence of Coronary Heart Disease. Epidemiological studies in other countries revealed a close correlation between an increase in the quantity of fat in the diet, an increase in serum cholesterol and an increase in Coronary Heart Disease. Racial factors seemed less dominant than dietary factors. A decrease in physical activity, smoking, and competitive, striving personality patterns were associated with an increased incidence of Coronary Heart Disease.

IV. Coronary Heart Disease must be prevented before the clinical disease becomes manifest, because approximately 50% of those men affected with the clinical disease die suddenly or within a relatively short time. The coronary prone individual may be detected by a history and physical emphasizing history of cigarette smoking, physical inactivity, personality patterns, and family history of Coronary Heart Disease. This is coupled with determinations of serum cholesterol, blood glucose, blood pressure, weight, and ECG. The susceptible person may then be treated by nutritional and pharmacological means, and by a change in living habits. Dietary treatment includes a diet moderate in total calories with the fats account-

ing for 30% of total calories, with a reduction in saturated fatty acids, and an increase in polyunsaturated fatty acids, and a decrease in dietary cholesterol. Such a diet would include skimmed milk, lean meat, fowl, fish, fruit, and vegetables, and would exclude butter, whole milk, cheese, cream, egg yolks, fat of meat, shortenings, margarines, and chocolate. Drugs used to reduce the serum cholesterol are triparanol, sitosterol, nicotinic acid, neomycin, and sodium dextrothyroxine, however these have not been accepted modes of therapy. The AMA Council on Food and Nutrition has not advocated changing the American diet to prevent Coronary Heart Disease.

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