Cardiac

Role of Risk Factors in Coronary Heart Disease: Significance for Primary Prevention

by

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INTRODUCTION

Although death from heart disease in the United States is declining, atherosclerotic diseases remain the foremost killer of Americans. Most cardiovascular deaths are due to coronary heart disease (CHD), but cerebral and peripheral vascular disease also contribute. Reasons for decreasing deaths from CHD and stroke have not been determined, nor do we know whether the severity of atherosclerosis in the U.S. population has been reduced. Atherosclerotic disease nonetheless continues to take an enormous toll in the U.S. and throughout much of the Western World; the disease is increasing in countries undergoing industralization.

The purpose of this review is to examine the concept that certain external factors, called "risk factors", contribute significantly to the frequency of CHD. It must be noted that CHD is the final product of a complicated chain of events starting with atherosclerosis and continuing with complications of atherosclerotic lesions leading to coronary occlusion (e.g. coronary thrombosis) and myocardial infarction. The risk factors thus could act on any of pathological processes leading to CHD. In the discussion to follow, a general classification of the risk factors will be considered. This will be followed by a description of the development of atherosclerosis with an emphasis on the processes that might be influenced by the risk factors. And finally, each of the categories of the risk factors will be examined in some detail.

The term "risk factor" has been used several ways in the past, and it is important to understand their meaning in relation to CHD. For example, some of the risk factors may directly cause atherosclerosis or its clinical complications producing CHD. These direct causes might be called "primary risk factors". Others may modify the primary risk factors, and thus affect atherosclerosis indirectly; these can be designated "secondary risk factors". Still others may not be direct or even indirect causes of CHD, but for various reasons may be correlated with increased risk for CHD; these could be called "tertiary risk factors".

Categorization of risk factors by this classification is difficult in some cases. Still, these are several strong candidates for primary risk factors for CHD. These include hypercholesterolemia (elevated levels of low-density lipoproteins), hypertension, smoking, and diabetes mellitus. High concentrations of low-density lipoproteins (LDL) probably contribute directly to formation of atheromatous lesions. For hypertension, smoking, and diabetes mellitus, circumstantial evidence for primary causality is strong, but mechanisms of their effects are not fully determined. Indeed, the atherogenic potential of these latter factors may not be entirely independent. In the presence of low levels of LDL, they may not greatly accelerate atherosclerosis; in the strictest sense, they may not be truly "primary," that is, they may be causative only in the presence of relatively high levels of plasma LDL. Nevertheless, when LDL concentrations are high, as commonly occurs in the U.S.A., hypertension, smoking, and diabetes probably deserve to be low called primary risk factors.

Another "primary" risk factor may be low concentrations of high-density lipoproteins (HDL), although this remains to be proven with certainty. More controversial is the claim that hypertriglyceridemia is a primary risk factor. Although high plasma triglycerides have been positively correlated with CHD in

several studies, the precise nature of this relationship remains to be defined, as will be discussed below.

The secondary risk factors are those that alter the primary factors. For instance, LDL concentrations can be increased in several ways. These include diets rich in saturated fats and cholesterol, obesity, genetic conditions, certain metabolic disease (e.g., hypothyroidism and the nephrotic syndrome), and drugs (e.g., thiazides). Also, the blood pressure can be increased by excess dietary sodium, obesity, and certain drugs and diseases. Finally, diabetes is made worse by obesity. One feature of the secondary risk factors is their variable influence on primary factors. For example, obesity raises the plasma lipids in some people but not others; the same true between dietary sodium and blood pressure.

Other factors may or may not fall into one of the aforementioned categories. For example, men and postmenopausal women are more prone to CHD than are premenopausal women, but the reasons for these differences are unclear. Likewise, we do not know why mental stress, certain personality types, and degree of physical activity seem to affect the risk for CHD.

Tertiary risk factors include a mesomorphic body build, corneal arcus, ear lobe creases, baldness, xanthomas, xanthelasma, and other stigmata of hypercholesterolemia, hypertension, smoking, and diabetes mellitus. A positive family history of premature atherosclerotic disease also belongs in this category. These characteristics do not themselves cause atherosclerosis or CHD, but they may signify a patient at increased risk.

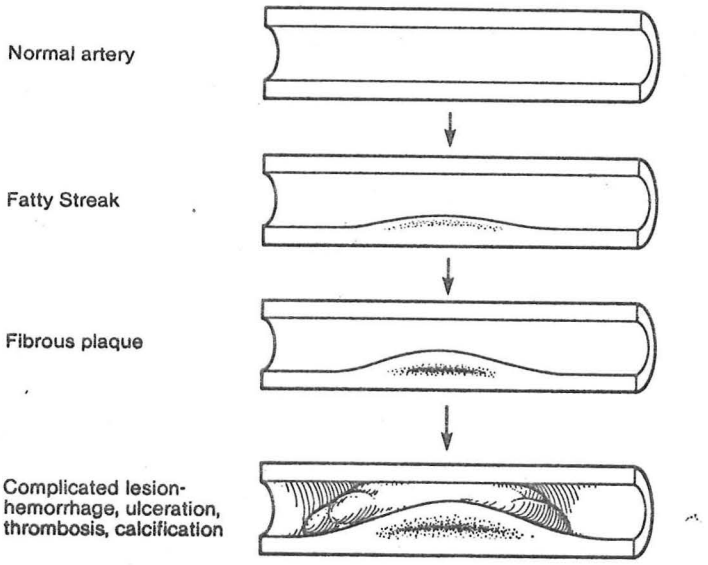
To understand fully the role of risk factors it is necessary to consider their effects on the atherogenic process, and to do this, the basic steps in the development of atherosclerosis--its pathology and pathogenesis must be reviewed.

PATHOLOGY AND PATHOGENESIS OF ATHEROSCLEROSIS

Gross pathology of atherosclerosis

One excellent classification of gross atherosclerotic lesions is that developed during the International Atherosclerosis Project (IAP) (McGill et al 1968). This classification is consistent with a pathogenetic sequence, but transformation of one type of lesion into another remains to be proven (Figure 1). Fatty streaks are the first lesions found in arteries. These lesions are flat to slightly elevated and stain with standard fat stains, Oil Red O or Sudan IV. Fatty streaks do not produce significant arterial narrowing. More severe lesions are the fibrous plaques, which are white, glistening, and elevated; they have a fibrous connective tissue "cap" covering a lipid-rich "core". These lesions can narrow the arterial lumen even to the point of complete occlusion. Fibrous plaques almost certainly can be transformed into "complicated" lesions; this is to say, fibrous plaques can become calcified or undergo hemorrhage, ulceration, or thrombosis.

Fig 1.—Gross pathology of atherosclerosis. First lesion is the fatty streak, a flat to slightly elevated lesion that stains with standard fat changes. Fatty streaks probably are converted into fibrous plaques. These are white, glistening, elevated lesions. They have a fibrous connective tissue cap covering a lipid-rich core, and they can narrow or occlude the arterial lumen. The final stage is the complicated lesion. It can contain calcification, ulceration, or intramural hemorrage or be the site of occlusive thrombosis.



Extensive knowledge about the distribution of atherosclerosis throughout the arterial system and in many different populations throughout the world was obtained in the IAP (McGill et al 1968). Atherosclerosis was quantified in the aorta and coronary arteries at 23,000 autopsies in 14 countries. Great variability was found in types, extent, and distribution of atherosclerotic plaques in different populations. The variability was mainly in fibrous plaques. The age of onset and extent of fatty streaks were similar for all populations under study. Fibrous plaques were most extensive in the white population of New Orleans, Louisiana, and Oslo, Norway; these lesions were much less common in people of Central and South America.

For the aorta, the abdominal portion always was more severely affected than the arch, regardless of population. Fatty streaks were first aortic lesions, and fibrous plaques generally appeared in the 30's and accelerated thereafter. Atherosclerosis in the aorta was most common on the posterior surface of the descending thoracic aorta at the orifices of the intercostal arteries, and in all areas of the abdominal aorta. For the coronary arteries, the left was involved most commonly near its bifurcation, and maximum atherosclerosis in the right coronary was just beyond the orifice. Fatty streaks and fibrous plaques were distributed similarly for the coronary arteries.

Most investigators believe that fatty streaks are precursors of fibrous plaques, but this relationship is not accepted universally. For example, the two types of lesions are not distributed identically in the aorta, and while rates of formation of fatty streaks are similar in all populations, there are wide discrepancies in rates of development of fibrous plaques and in their severity. Therefore, different factors may affect the pathogenesis of fatty streaks and fibrous plaques.

Microscopic pathology of atherosclerosis.

Fatty streaks are the first well-defined microscopic lesion of atherosclerosis (Figure 2). The first changes leading to the fatty streak are accumulation of cells containing lipid droplets (foam cells) in the subintimal region (Haust 1977, 1978). Finely-dispersed extracellular lipid also is present in these lesions. In larger fatty streaks, there is a progressive accumulation of foam cells extracellular lipid, and fibrin can be detected in extracellular spaces.

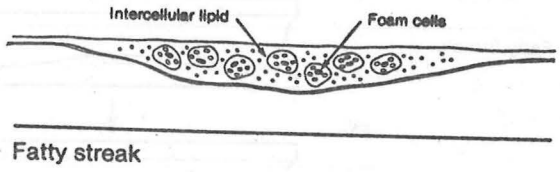


Fig. 2 Microscopic pathology of fatty streak. Two changes are noted. First, there is accumulation of cells containing lipid droplets (foam cells) in the subintimal region. Also, finely dispersed extracellular lipids are present.

Although lipid accumulation in the subintimal region is the first change noted by routine microscopy, some investigators believe that other alternations in the arterial wall precede the fatty streak. For instance, a gelatinous change resulting from focal intimal swelling and intimal edema has been noted (Haust 1971, 1978). This change possibly could signify endothelial injury. Whether these gelatinous lesions are true precursors to more-advanced plaques is unknown. Another early change may be microscopic mural thrombi (Haust 1971, 1978); small thrombi that consist of varying amounts of platelets and fibrin have been observed on "normal" intima. Eventually these thrombi become organized and covered by endothelium.

Fibrous plaques. The microscopic appearance of the fibrous plaque is complex and variable (Haust 1971, 1978). Its essential structure consists of a lipid-rich core beneath a fibrous connective tissue cap (Figure 3). The core contains cholesterol crystals, other lipids, proteoglycans, fibrin, various proteins, and calcium. The fibrous cap has smooth muscle cells, collagen, extracellular and intracellular lipids, including foam cells. The connective tissue of the fibrous cap contains ground substance, reticulum fibrils, and collagenous and elastic fibers, while its surface sometimes is covered by a mural thrombus. It is possible that these thrombi become organized and are incorporated into the substance of the fibrous cap. Foam cells tend to be concentrated in the base of the fibrous cap, while in the upper subintimal areas, the smooth muscle cells contain less lipid. As fibrous plaques grow, they eventually undergo calcification, followed by ulceration, hemorrhage, and occlusive thrombosis.

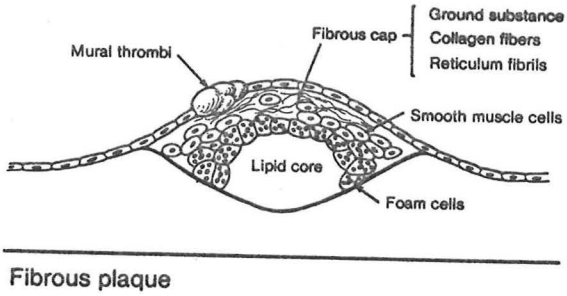


Fig. 3. Microscopic pathology of fibrous plaque. The fibrous plaque has a fibrous cap containing ground substance, collagen fibers, and reticulum fibrils. Mural thrombi sometimes are present. In the periphery are smooth muscle cells showing evidence of transformatino into foam cells or connective tissue-secreting cells. The center of the lesion is a core of necrotic material containing large quantities of extracellular cholesterol and other lipids.

Chemistry of atherosclerotic lesions

The most striking constituent of atherosclerotic lesions is lipid. Approximately 40% of the dry weight of fatty streaks and 60% of fibrous plaques are lipids (Smith 1974). In the normal intima of young children, very little lipid can be demonstrated by sudan staining (Smith 1974) and the intimal lipids at this age is in a single phase--a phospholipid layer. With aging, especially after 30 years, there is a progressive accumulation of fine, extracellular, perifibrous lipid droplets. The number of these lipid droplets correlates with the concentration of most lipid classes (Smith 1974). Cholesterol ester is a minor constituent of normal intimal lipids for the first 30 years of life; thereafter it becomes the major component (Smith 1974). Concentrations of unesterified cholesterol also increase continuously with age; they do not however show dramatic increases after 25-30 years that are noted for cholesterol esters.

The types of fatty acids of cholesterol ester in normal intima are revealing. Ratios of linoleic acid to oleic acid in cholesterol esters are low early in life. The linoleic/oleic ratio increases progressively until the two fatty acids are present in about equal proportions by age 20; thereafter, the ratio in normal intima remains constant despite a continuous increase in cholesterol ester content. The relative contents of linoleic acid and oleic acid in esters of arterial wall cholesterol are significant for two reasons. First, they suggest a distribution between intra- and extracellular esters; intracellular cholesterol is esterified largely with oleic acid while extracellular cholesterol contains mostly in linoleic acid esters. The presence of linoleic acid in cholesterol esters also suggests a plasma origin; a high portion of plasma cholesterol esters contain linoleic acid.

Fatty streaks have many foam cells. These cells have many cytoplasmic lipid droplets containing cholesterol esters; these droplets are not enclosed by membranes. Cholesterol esters of fatty streaks have a high ratio of oleic to linoleic acid which implies that esterification took place within the cells. Fatty streaks are relatively low in free cholesterol and triglycerides (Smith 1974).

Fibrous plaques have a gruel-like center containing necrotic tissue packed with cholesterol crystals. Much of the cholesterol is unesterified. The cholesterol esters that are present are rich in linoleic acid, suggesting that they arose from circulating cholesterol which also is rich in cholesterol esters (Smith 1972). Relatively large amounts of sphingomyelin also are present in the lipid core of plaques, and because of the relative enrichment of the plasma phospholipids with sphingomyelin, a plasma origin of plaque lipid also is suggested.

"Intermediate" lesions. Katz, Shipley, and Small (Katz et al 1976) have chemically analyzed atherosclerotic plaques of several different types, and their evidence suggests that fatty streaks are converted into fibrous plaques. They analyzed lesions that grossly appeared to be fatty streaks, but these lesions had a chemical composition intermediate between ordinary fatty streaks and advanced plaques. These "intermediate" lesions contained considerable amounts of unesterified cholesterol, and they seemed to correspond to the "fatty plaque" described earlier by Smith and Starter (Smith et al 1972). The "fatty plaque" could be dissected into three parts. The region immediately beneath the lumen contained intact cells that were filled with lipid and are devoid of necrosis; a second layer just below had fat-filled cells showing early degeneration. And below this layer were necrotic cells and extracellular lipids. Small (Small 1977) has offered the following interpretation of this pattern: when foam cells acquire a critical amount of cholesterol, their esterification mechanisms fail. Unesterified cholesterol begins to accumulate, and when the concentration reaches saturation, cholesterol crystallizes and kills the cells. The dying cells then release their cholesterol crystals into the necrotic core of the lesion.

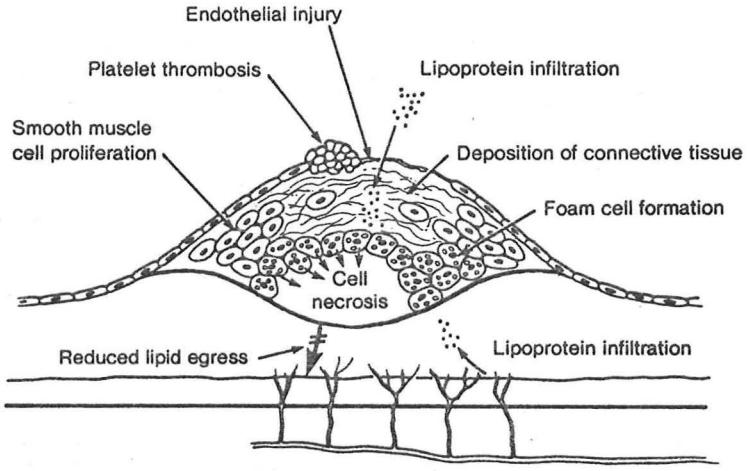
Lipoproteins in atheromatous plaques. In fibrous plaques, cholesterol esters contain mostly linoleic acid, similar to the pattern found for cholesterol ester. A plasma origin of these esters is made more likely by the recognition that lipoproteins from plasma can be seen in plaques. The major lipoprotein in the lesions is low density lipoprotein (LDL); it has been recognized immunologically by an antibody against its protein constituent, apolipoprotein B (Kao et al 1968, Smith et al 1971, Walton et al 1968, Hoff et al 1975, 1979, 1979). Concentrations of LDL protein in lesions correlate well with plasma concentrations (Smith 1977). Amounts of LDL and another large molecule, fibrinogen, in the intima exceed those of albumin (Smith 1977); larger molecules thus seem to be delayed in their clearance from the arterial wall.

Evolution of the atherosclerotic plaque.

Several different processes contribute to formation of fatty streaks and fibrous plaques. These processes seem to be interdependent; they act in concert for plaque development once a lesion is initiated. They apparently act as a viscous cycle to produce discrete lesions; thus, formation of plaques appears to result from self-perpetuating events. The result is a segmental distribution of

lesions. The essential features in evolution of lesions are shown in Figure 4; each of these can be discussed individually.

Fig. 4 Evolution of atherosclerotic plaque. The major processes postulated for plaque development are shown here. They include injury to endothelium with loss of protective endothelial barrier, lipoprotein infiltration from the luminal side, platelet thrombosis, smooth muscle proliferation, foam cell formation, deposition of connective tissue, reduced egress of lipids from the vasa vasorum, and perhaps, lipoprotein infiltration through the capillaries of the vasa vasorum.



Endothelial injury. The endothelium is a barrier separating the subintimal regions of arteries from blood constituents; its integrity seems essential to minimize the development of plaques. If the endothelial lining is disrupted, at least two events theoretically could initiate the formation of lesions: these are platelet thrombosis and enhanced infiltration of plasma lipids.

Despite these comments, a role of endothelial injury in the initiation of the human lesion remains to be established with certainty. There is no proof that loss of endothelium is the initial lesion of atherosclerosis in man. This hypothesis nevertheless is attractive. When endothelial damage is induced in experimental animals by several means (e.g., mechanical damage, changes in temperature, pH, osmolarity, and irradiation (Stemerman 1979, Constantinides et al 1969, Fry et al 1972, Moore 1973, Kirkpatrick 1967)) subintimal changes suggestive of early atherosclerotic lesions result (Stemerman et al 1977, Minick et al 1977) or experimental atherosclerosis can be accelerated (Friedman et al 1965). Several injurious factors causing endothelial damage have been postulated for humans: endothelial damage from endotoxins (Gaynor et al 1970, 1971), hyperlipidemia (Ross et al 1976), antigenantibody complexes (Minick et al 1966), carbon monoxide (Mustard et al 1963), viral infection (Burch 1974), and hemodynamic stresses.

Hemodynamic stresses. Since atherosclerosis occurs preferentially at certain sites in the arterial tree, local hemodynamic factors could influence plaque development (Glagov 1972). Typical sites of involvement, as near branch points of arteries, seem to be sites of unusual lateral stress, and this stress could sheer off the endothelial lining, and set the stage for lesion growth.

Circulating factors. Endothelial injury remains to be proven the initial lesion of plaque formation. Several factors nonetheless can damage vascular endothelium in so doing, and theoretically could be atherogenic. These include

toxic bacterial products (endotoxins), viral infections, drugs, and deposition of antigen-antibody complexes. Systematic lupus erythematosus has been reported to accelerate atherosclerosis, possibly because circulating immune complexes associate with this disorder damage endothelial cells. High concentrations of carbon monoxide in blood of smokers also may be injurious (Mustard et al 1963), as could unidentified chemical toxins circulating in chronic renal failure. Reports that high concentrations of plasma lipoproteins are "toxic" to endothelial cells, and thus may contribute to accelerated atherosclerosis in hyperlipidemic patients, are intriguing (Ross et al 1976). Increased thromboembolism has been claimed for patients with homocystinuria (Harker et al 1974), and patchy desquamation of arterial endothelium has been produced in baboons by maintenance of high levels of homocystine for several days (Harker et al 1974). Along the same lines, atherosclerosis can be caused in rabbits by large amounts of other sulfur-containing amino acids -- methionine, homocysteine, and homocysteic acid (McCully et al 1975). Finally, a variety of vasoactive amines have been employed to alter endothelial cells under experimental circumstances, and they have been implicated in the initiation of atherosclerosis (Constantinides et al 1969).

Smooth muscle cell proliferation.

Following endothelial injury in experimental animals, of the arterial wall undergo proliferation. Smooth muscle cells apparently the major cell type in atherosclerotic plaques, and factors responsible for their proliferation may be of importance great interest. Several factors can stimulate the growth of smooth muscle cells. Perhaps the most important is derived from the platelet. The usual response to endothelial injury is formation of a platelet thrombus (Stemerman et al 1979); platelets adhere to damaged endothelium, aggregate, and produce an adherent thrombus. In the process they release a mitogenic factor called a platelet-derived growth factor (PDGF) (Ross et al 1974, 1978, Moss et al 1975). This factor stimulates growth of smooth muscle cells in tissue culture, and it may induce their proliferation *in vivo* in response to endothelial injury. Other growth factors, especially one derived from macrophages (Moss et al 1975), similarly can induce proliferation of smooth muscle cells.

The possibility that smooth muscle cells can proliferate with endothelial injury has been suggested by Benditt et al (Moss et al 1975, Schwartz et al 1976, Benditt 1976, 1978). These workers believe that most smooth muscle cells in atherosclerotic lesions are monoclonal, i.e. they are derived from a single cell line. Their belief is based on their finding of unique enzymatic pattern in cells which is not found in "polyclonal" smooth muscle cells of the normal arterial media. Benditt et al (Moss et al 1975, Schwartz et al 1976, Benditt 1976, 1978) postulate that proliferation of smooth muscle cells in the atherosclerotic plaque resembles a neoplastic response similar to monoclonal leiomyomas of the uterus. The monoclonic pattern of cells of course reveals nothing about the nature of the stimulus, viral or otherwise. Many investigators furthermore do not occur that this proliferation is truly neoplastic: one cell line may simply outgrow the others in response to the underlying stimulus.

Plasma lipid infiltration.

Another major process in development of atherosclerosis is infiltration of plasma lipids, especially cholesterol. Since lipids are insoluble in aqueous

solutions, special mechanisms are required for their transport. These consist essentially of lipid-protein complexes called lipoproteins. Compared to other plasma proteins, the lipoproteins are relatively large, and their large size limits their filtration into the arterial intima. The endothelial barrier may be the crucial factor reducing lipoprotein infiltration, and the significance of this barrier must be considered.

The intimal endothelial barrier seemingly delays but does not prevent the entry of lipoproteins into subintimal spaces. The plasma proteins including lipoproteins are able to penetrate intact endothelium (Reichl et al 1973, Bratzler et al 1977, 1977, 1977), but the rate of filtration is restricted by this barrier. Loss of endothelium allow the plasma lipoproteins to infiltrate freely into the arterial wall. Studies in experimental support the animals importance of loss of the endothelial barrier; cholesterol-induced atherosclerosis in animals is enhanced greatly by experimental endothelial damage (Friedman et al 1965).

Role of the vasa vasorum. Exactly how do lipoproteins enter the arterial wall? Most investigators have assumed that they transverse the intimal lining and thereby enter the subintimal space (Page 1954, Adams 1967) more consideration should be given to the role of the microcirculation in development of plaques. First, susceptibility to atherosclerosis could be affected by the "primary" vascularization of the arterial wall (Higginbotham et al 1963, Winternizt et al 1938, Wolinsky et al 1967, Geiringer 1951, Wilens 1957, Robertson 1929, Schlichter 1946, 1946, 1949, Mahley et al 1977, Cliff 1976, Schlichter et al 1949, Leary 1938), that is, the microcirculation (arterial, venous, and lymphatic) arising in the adventitia and penetrating the outer third of the media (Cliff 1976) (Figure 5). In the absence of diffuse intimal thickening, this vascularization (the vasa vasorum rarely extends into the inner media (Geiringer 1951, Leary 1938). When intimal thickening is present, it can enter the inner media (Figure 6) (Geiringer 1951).

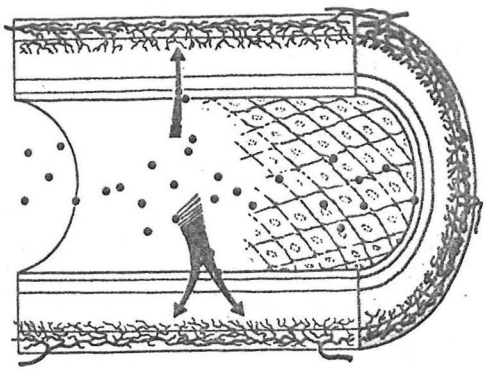
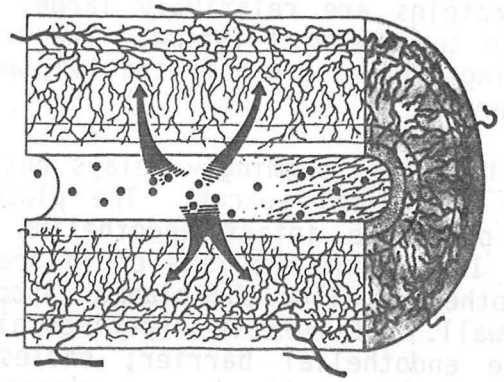


Fig 5 —Cross section of a normal, nonthickened artery. Vasa vasorum penetrate the adventitia and outer third of the media. The intima has no vascularization. Lipoproteins enter the wall from the circulation; they pass through intima and out of the arterial wall via the adventitial vasa vasorum.

Fig. 6.-Cross section of artery with significant thickening of the intima but without atheroma. Vasa vasorum penetrate completely into the media and partially into the intima. Lipoproteins enter the intima from the lumen and pass out via the vasa vasorum.



The inner wall of the artery is avascular, (Geiringer 1951 Wilens 1957, Robertson 1929, Schlichter 1946, 1949) and consequently, mechanisms by which cholesterol enters and leaves the subintimal space must be important in atherogenesis. All cholesterol in this region presumably must leave the arterial wall via the lymphatic channels of the vasa vasorum. If these channels are underdeveloped or defective in certain arterial segments, accumulation of cholesterol in the intima of these segments might be expected to be increased. The density of microvessels in the adjacent media indeed has been correlated to susceptibility to atherosclerosis among different species. The density of primary vascularization is greatest in the dog and is progressively less in human beings, chickens, and rabbits (Schlichter et al 1949); of interest, resistance to atherosclerosis appears to follow this same sequence. Rabbits, the species with the least primary vascularization, are the most susceptible to diet-induced atherosclerosis (Schlichter 1946). Furthermore, destruction of the vasa vasorum in the dog, which has the most, also renders this animal more susceptible to atherosclerosis induced by dietary cholesterol (Schlichter 1949).

The intimal-filtration theory, which has been accepted by most investigators, can readily explain the development of the fatty streak. Filtration of plasma lipoproteins across a normal or damaged endothelium lining the lumen can explain accumulation of lipids in the subintimal region, (Adams 1967) but continued deposition of cholesterol in fibrous plaques is more difficult to explain by the intimal-filtration theory. The fibrous cap of these lesions seemingly should act as a barrier to continuous filtration of lipoproteins down to the zone where cholesterol accumulates. How then does cholesterol continue to accumulate in the lipid core of the fibrous plaque? One possibility is that progressive accumulation occurs from below, i.e. from leakage out of the capillaries of the vasa vasorum. By this mechanism, an accumulation of cholesterol could occur in advanced atherosclerotic lesions with large fibrous coverings.

Cholesterol accumulation in advanced plaques could occur in still another mechanisms. The blood supply in the region of atherosclerotic plaques is complicated and abnormal (Winternizt et al 1938, Geiringer 1951, Leary, 1938, Duguid 1955, Patterson 1936, 1938). In essence, a secondary blood supply develops within the arterial wall, and an extensive system of vasa vasorum in the inner media and thickened intima an extensive system of vasa vasorum is

formed. Some of these microvessels apparently arise by proliferation into the intima from the adventitia (Geiringer 1951), but other vessels enter from the lumen.

This so-called secondary vascularization might allow for delivery of lipids to the center of the fibrous plaque. For example, vessels might penetrate into and beneath the fibrous cap and thereby permit exudation of lipoproteins into the core of the lesion. The rate of effusion of lipoproteins from secondary vessels might be enhanced by an imperfect formation of the vascular structure (Higginbotham et al 1963). Secondary vessels frequently are nothing more than simple tubes of endothelial cells with no supporting connective tissue and no basement membranes. The capillaries in this system are larger, more collapsible, and more fragile than normal capillaries. The vessels frequently are occluded by thrombotic material. These vessels likewise could supply lipoproteins to the core of the plaque, and they also could permit diffusion of platelet-derived growth factor into the arterial wall thereby stimulating proliferation of smooth muscle cells (Ross et al, 1974, 1978, 1978, Rutherford et al 1976).

Figure 7 summarizes this proposed microvascular hypothesis of atherosclerosis. The arterial microcirculation might accelerate atherogenesis by at least three mechanisms. First, injury to arterioles or to arteriolar capillaries should permit increased effusion of lipoproteins into the subintimal tissue (Figure 7A); second, when primary vascularization is sparse, exit of cholesterol from the subintimal space may be retarded (Figure 7B); and third, defective secondary vascularization in established plaques may be another source for lipoproteins (Figure 7C).

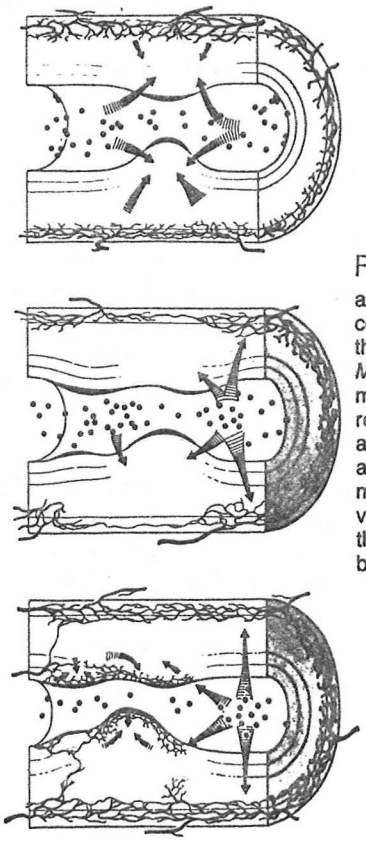


Fig. 7.--Cross sections of atheromatous arteries. *Top*, leaky vasa vasorum contribute to the influx of lipoproteins into the intima, accelerating plaque formation. *Middle*, inadequately developed, medioadventitial vasa vasorum prevent removal of lipoproteins, resulting in lipid accumulation. *Bottom*, advanced atherosclerotic plaque with second microvascularization. Influx of lipoproteins via the secondary vessels could increase the rate of atheroma growth. (Reproduced by permission.[61])

Deposition of collagen and other extracellular constituents.

During the course of lesion development, smooth muscle cells are transformed from contracting cells into cells that synthesize and secrete connective tissue proteins (Ross 1981). This transformation probably is the result of a decrease in cell density (Ross 1981). As smooth muscle cells migrate in the direction of damaged endothelial, perhaps attracted by chemotatic factors released from platelet thrombi, their density decreases and they undergo transformation into a fibroblast-like cell. The resulting cell begins to secrete connective tissue materials which contribute to the fibrous cap.

The fibrous cap contains a mixture of collagen and other fibers and ground substance (Robinson et al 1975). The latter consists mainly of large polymers of carbohydrates named glycoaminoglycans (GAG), mucopolysaccharides, and acid mucopolysaccharides. Several varieties of GAG have been characterized including chondroitin-4-sulfate, chrondrotin-6-sulfate, dermatan sulfate, heparin, heparin sulfate, and keratosulfate. The molecular weights of different GAGs are very large. In fact these molecules represent essentially a continuous network of interlacing molecular chains. These carbohydrate polymers of ground substance are covalently linked to protein; the products have been designated proteoglycans. GAGs are intimately bound to connective tissue fibers. The formation of collagen fibers is thought to occur by chemical interaction between soluble procollagen secreted by fibroblasts and GAGs of the interstitial ground substance. In essence collagen fibers represent many small collagen fibrils that have been cemented together by GAG. The deposition of connective tissue in response to injury is thought to pass through stages. In the early period the ground substance predominates and collagen fibers are few; as the lesions mature the number of collagen fibers increase and ground substance disappears.

GAGs could play an important role in atherogenesis because of their ability to bind low density lipoproteins. The polymers resemble heparin which is known to selectively precipitate these lipoproteins. During filtration of lipoproteins through the arterial wall they might become entrapped by interaction with GAG.

Foam cell formation.

The characteristic cell in the atherosclerotic plaque is the lipid-laden cell, or foam cell. This cell can be derived from either smooth muscle cells or macrophages (Ross 1981). The relative contribution of the two types of cells to the overall foam cell population of plaques have not been determined, but most investigators believe that smooth muscle cells predominate. Recent investigations nonetheless indicate that macrophages constitute a significant portion of foam cells (Ross 1981).

The cellular and molecular events leading to foam cells are not well understood. It is assumed that they are the result of uptake of plasma lipoproteins that have infiltrated the arterial wall. Uptake of lipoproteins by cells can occur by at least two different mechanisms. One way involves cell surface receptors for lipoproteins, particularly low density lipoproteins (Goldstein et al 1982). These lipoproteins bind to receptors, and the receptor-lipoprotein complex is internalized and enters lysosomes. In the lysosomes the constituents of the lipoprotein are degraded by hydrolytic enzymes: the proteins are hydrolyzed to amino acids, and the lipids are broken down to their

constituent parts. In particular, cholesterol esters are hydrolyzed to unesterified cholesterol and a fatty acid. The cholesterol then enters the cytoplasma of the cell where it can have three different fates. It can be used for the production of membranes; it can inhibit the cell's own synthesis of cholesterol; and it can be reesterified with a fatty acid and stored in the cell as cholesterol ester. However, the accumulation of cholesterol in cells through the receptor-mediated pathway seemingly is insufficient to produce foam cells. This is because any increase in cellular cholesterol leads to a reduction in synthesis of receptors for lipoproteins. In other words, the receptor pathway seems highly regulated to maintain optimal concentrations of intracellular cholesterol (Goldstein et al 1975).

The formation of foam cells most likely is the result of uptake of lipoproteins by a second pathway, the nonreceptor-mediated pathway. Several types of nonreceptor mechanisms may exist (Goldstein et al 1982, Brown et al 1980, 1979, Goldstein et al 1979). One of these is bulk-phase endocytosis in which lipoproteins are ingested as a component of extracellular fluid engulfed by cells. Another mechanism is the uptake of modified lipoproteins through a pathway independent of receptors (Brown et al 1980, 1979, Goldstein et al 1979). Seemingly, these latter two pathways are not inhibited by increasing concentrations of intracellular cholesterol; cellular uptake thus continues unabated despite progressive accumulation of cholesterol in cells. The final result is a large number of cholesterol-filled droplets (Goldstein et al 1979). Cholesterol in these droplets is esterified primarily with oleic acid; this indicates that the lipoprotein-cholesterol ester is hydrolyzed before being reesterified and stored.

RISK FACTORS FOR CORONARY HEART DISEASE

Establishment of risk factors.

The notion that certain behavior characteristics, physical signs, or chemical measurements are associated with increased risk for coronary heart disease has received strong support for several types of studies. These characteristics are called risk factors, and their causal link to CHD has been obtained in several ways. To understand the nature of the risk factors in the causation of CHD, the way in which the link way established must be understood. Each type of study can be reviewed briefly.

Clinical investigation. A strong clinical impression of a risk association can be obtained from study of individual patients. For example, many patients with severe hypercholesterolemia have very premature atherosclerosis. The same is true for patients with severe hypertension, diabetes mellitus, and heavy smokers. These clinical impressions suggest associations but do little to establish a causal relationship; better evidence is needed.

Epidemiological studies. The clinical impressions have given way to epidemiological studies which give a stronger scientific basis for risk-associated disease. In the United States, the major epidemiological studies have been the Framingham Heart Studies, the Pooling Project, and the Multiple Risk Factor Intervention Trial (MRFIT). These within-populations studies (i.e. within the American public) have demonstrated an independent relation of hypercholesterolemia, hypertension, diabetes mellitus, smoking, and

more recently, obesity to risk for CHD. These same relationships have been supported by cross cultural studies, such as the Seven Country Study and the Ni-Hon-San study. The latter provide strong evidence of a relationship between plasma cholesterol levels and CHD. These are only a few of many epidemiological studies that establish the validity of the risk factor theory.

Pathological studies. While the epidemiological studies reveal a relation between risk factors and rates of CHD, autopsy studies are needed to prove a connection between risk factors and the degree of atherosclerosis. The well-known International Atherosclerosis Project (IAP) provides strong evidence of differences between the type and degree of atherosclerosis in different populations. Unfortunately, this study, which was retrospective in nature and had limited resources, did not provide much information about risk factors and their relation to the severity of atherosclerosis. More recently, other large autopsy studies have paid more attention to risk factors, and they have provided a better correlation between risk factors and atherosclerosis. Besides the IAP, these studies have been carried out in New Orleans, Malmo Sweeden, Oslo Norway, Puerto Rico, Honolulu, and Framingham Mass. The essential characteristics of these trials are outlined in Table 1.

Table 1

AUTOPSY STUDIES

Study	Size of Cohort	No. of Cases	% of all Deaths	Authors
Intern. Ath. Project	NA	21,302	NA	
New Orleans	NA	1,292	52%	Strong et al 1978,1980
Olso	16,232	129	46%	Solberg et al 1980
Malmo	703	46	50%	Sternby 1980
Puerto Rico	9,824	139	14%	Sorlie et al 1981
Honolulu	8,006	137	28%	Rhoads et al 1978
Framingham	5,209	127	14%	Feinleib et al 1979

Angiography. In recent years, with the upsurge in the number of coronary angiograms performed, there has been the opportunity to estimate the severity of atherosclerosis and relate it to the presence of various risk factors. Although this approach has obvious advantages over autopsy studies for definition of risk factors, it is hampered by the difficulties of quantifying lesion size by angiography. However, in recent years, remarkable advances have been made in the technology of lesion measurements, and this approach offers new opportunity for determining the significance of different risk factors on the pathological processes leading to CHD.

A multitude of "risk factors" have been proclaimed, but several stand out as being major factors. Most of these appear to play an important causative role in atherogenesis, but in truth, their precise relationship to CHD has not been determined fully. In this review, major coronary risk factors will be examined for their role in causation, the mechanisms involved, and the strength of the relationship.

LIPIDS AND LIPOPROTEINS

Most of cholesterol in atherosclerotic plaques comes from the plasma cholesterol. The cholesterol in plasma is carried in unique lipid-protein complexes called lipoproteins. The discovery of lipoproteins opened a new era in the study of the pathogenesis of lipoproteins. Several types of lipoproteins are present in plasma, and each may have a different atherogenic potential. Each form of lipoprotein also appears to have unique functions. The major function of lipoproteins overall is to transport the two predominant lipids of plasma--cholesterol and triglycerides--from one organ (or tissue) to another. While the transport of lipids is the primary function of lipoproteins, this function is performed by the proteins, or apolipoproteins, of the lipoproteins. The apolipoproteins in fact have several functions including solubilizing lipids for secretion and transport, activating lipases and other transfer enzymes, and acting as ligands for receptor-mediated clearance of lipoproteins.

The amount of cholesterol transported in plasma is a function of the overall metabolism of cholesterol, i.e. the amount of cholesterol absorbed by the intestine, amounts synthesized by the various tissues of the body, amounts degraded into bile acids, and rates of cholesterol excretion. All of these may affect the metabolism of lipoproteins and thus indirectly affect atherogensis.

In the discussion to follow, the metabolism of different lipoproteins and lipoproteins will be considered in more detail and the metabolism of cholesterol also will be discussed.

Lipoprotein metabolism.

As indicated above, the major sources of cholesterol in atherosclerotic lesions are the plasma lipoproteins. To understand the role of lipoproteins in atherogenesis it will be necessary to review some of the major pathways of lipoprotein metabolism. There are several types of lipoproteins, and each may have a different atherogenic potential. The major function of lipoproteins is to transport the two major lipids of plasma -- cholesterol and triglycerides -- from one organ (or tissue) to another. Two major organs -- liver and intestine -- produce lipoproteins (Figure 8). Intestinal lipoproteins (chylomicrons) transport newly-absorbed dietary fat (triglycerides). Hepatic lipoproteins deliver cholesterol and triglycerides to peripheral tissues. The major lipoproteins and their functions can be reviewed briefly.

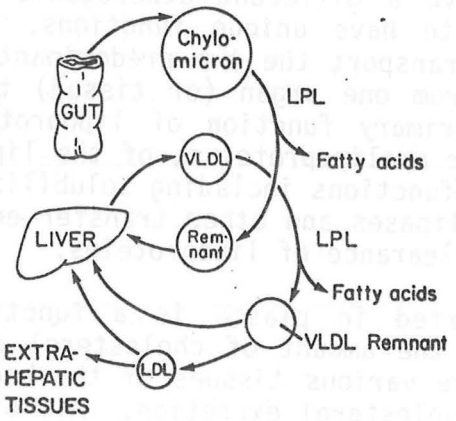


Fig. 8.
-Metabolism of chylomicrons and lipoproteins (see text for description of pathways).

Chylomicrons, formed in intestinal mucosa, pass through the thoracic duct, enter the systemic circulation, and become distributed throughout the peripheral circulation. As chylomicrons enter capillary beds they come into contact with an enzyme, lipoprotein lipase, located on the surface of endothelial cells. At this site, triglycerides undergo hydrolysis to fatty acids and glycerol. Newly-released fatty acids enter the circulation attached to albumin; they can be used for energy by peripheral tissues, they can be stored in adipose tissue as triglycerides, or they can be taken up by the liver. After lipolysis is almost complete, a chylomicron "remnant" is released back into the circulation and is cleared rapidly by the liver. Chylomicron remnants contain the cholesterol absorbed along with triglycerides.

Very low density lipoproteins (VLDL). The liver produces triglyceride-rich particles called very low density lipoprotein (VLDL). VLDL are smaller than chylomicrons, but their metabolism is similar. They undergo interaction with lipoprotein lipase on the surface of capillary endothelial cells; a release of free fatty acids is the result. Lipolysis of triglycerides produces a VLDL remnant. VLDL remnants are removed by the liver in many animal species. In normal persons, on the other hand, most VLDL remnants are catabolized further to smaller lipoproteins.

Low density lipoproteins (LDL) are largely the product of the catabolism of VLDL and VLDL remnants. They are rich in cholesterol ester and contain only small amounts of triglycerides. LDL is the major cholesterol-carrying lipoprotein in plasma of normal people. It can be removed from the circulation by either the liver or peripheral tissues. Uptake of LDL can occur by receptor-mediated or non-receptor pathways (Goldstein et al 1982). The receptor pathway appears to be responsible for removal of most LDL (perhaps 70-80%) while nonreceptor removal is responsible for the remainder (Goldstein et al 1982).

High density lipoproteins (HDL) are the smallest lipid-containing particles in plasma. They are rich in cholesterol esters and normally contain only small amounts of triglycerides. Two major fractions of HDL have been identified: a larger HDL_2 and a smaller HDL_3 (Krause 1982). The origins of HDL are complex. Both the lipid and protein components of these lipoproteins apparently are in a state of constant flux, moving from one lipoprotein to another. The major function of HDL may be to shuttle cholesterol between tissues and other lipoproteins.

Apolipoprotein metabolism.

In recent years there as been an increasing interest in the proteins responsible for the transport of lipids. These proteins are called apolipoproteins (apoproteins), and they may be associated intimately with the atherogenic process. For this reason they need to be explained briefly.

Apoprotein B (apo B). Two major proteins belong to the apo B family. The smaller apo B, also named apo B-48 because of its electrophoretic characteristics, is the major structural apoprotein of chylomicrons (Malloy et al 1982). Apo B-48 is a nonexchangeable apoprotein and thus remains on chylomicrons throughout their metabolism. Hepatic cell receptors for chylomicron remnants may recognize the apo B-48 moiety on these particles.

The larger form of apo B is B-100 (Malloy et al 1982). It is the major structural apoprotein of VLDL and LDL, and remains with these lipoproteins for the duration of their life in the plasma compartment. Apo B-100 is large and highly-insoluble making its study difficult. This apoprotein seemingly plays a crucial role in LDL metabolism, and is the recognition site on LDL for interaction with LDL receptors.

C apoproteins. Hydrolysis of triglycerides in VLDL and chylomicrons requires the presence of other apoproteins on the surface of these lipoproteins. The C apoproteins are one such family. These apoproteins modulate the activity of lipoprotein lipase (LPL). Apo C-II activates LPL (Bier et al 1970, Ekman et al 1975, Havel et al 1973). Its absence prevents normal lipolysis and causes hypertriglyceridemia (Cox et al 1978). Apo C-III seemingly retards catabolism of TG-rich particles (Ekman et al 1975). The ratio of apo C-II to apo C-III thus may influence rates of catabolism of VLDL and chylomicrons. When these lipoproteins undergo lipolysis the apo C's are lost from their surface; they attach to HDL, only to be recycled to newly-secreted, TG-rich lipoproteins.

E apoproteins. Another series of apoproteins on VLDL and chylomicrons are of the apo E's. These peptides are particularly rich in arginine. They are required for normal catabolism of remnants. The liver has receptors that recognize apo E on remnants (Hui et al 1981); the interactions between apo E and its receptor on the liver is the first step in clearance of remnants from the circulation. Apo E likely participates in the conversion of VLDL to LDL. This conversion also may require attachment of the remnant to its receptor on the liver cell (Havel 1982). The final step in transformation of VLDL to LDL may occur at this site.

Apo E can be separated into several isoforms by electrophoresis. Recent work indicates that three genes E^2, E^3, and E^4, code for the different isoforms (Havel 1982). Each person has two alleles for apo E synthesis, and six

different genotypes therefore are possible. One of these types, E^2E^2, is associated with defective catabolism of remnants. Patients who have this genotype have an accumulation of remnants from both VLDL and chylomicrons in plasma (Havel 1982).

A apoproteins. These apoproteins are found almost exclusively with HDL. The two major types are apo A-I and apo A-II (Krause 1982). They are soluble in plasma and are transferred readily from one HDL particle to another. They have a high affinity for cholesterol and may play a major role in removing excess cholesterol from the surface of cells. Consequently the cholesterol extracted from cells probably enters first into HDL.

The metabolism of the major lipoproteins and their apolipoproteins is outlined in Figure 9. The liver secretes TG-rich particles called very low density lipoproteins (VLDL). Stalenhoef et al. (1984) have shown recently that very large VLDL containing apoB-100 behave as chylomicrons; that is to say, they are cleared rapidly from the circulation, possibly being removed by hepatic apoE receptors. Other and presumably smaller VLDL are degraded by lipolysis to longer-lived VLDL remnants (Figure 9). These remnants can have two fates: they can be removed by the liver or be converted to low density lipoproteins (LDL). In experimental animals (Hui et al 1981, Goldstein et al 1983), and almost certainly in humans, VLDL remnants of this type are cleared by hepatic cell-surface receptors that recognize apoB-100. However, uptake of VLDL remnants appears to be accelerated by the presence of apoE, and hence the receptors have been called B/E receptors (Hui et al 1981) or B-100/E receptors (Havel 1982). The steps in conversion of VLDL remnants to LDL are not well understood. Havel (1982) has postulated that the liver is required for this conversion; if so, hepatic triglyceride lipase (HTGL) may hydrolyze the remaining core TG as well as the excess surface-coat phospholipids of the remnants.

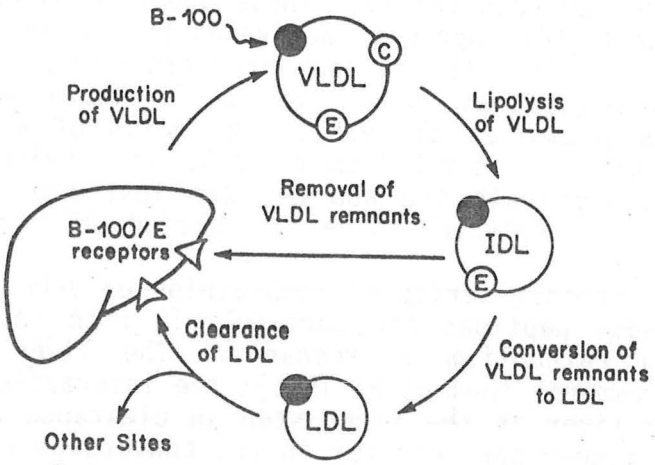


Fig. 9. Major steps in the metabolism of lipoproteins containing apoB-100. Production of VLDL-apoB-100 is by the liver. Lipolysis of VLDL-TG occurs via lipoprotein lipase (LPL). The resultant VLDL remnants, or intermediate density lipoproteins (IDL), can have two fates. They can be cleared by the liver via apoB-100/E receptors or be converted to LDL. LDL likewise can be removed by the same receptors, either in the liver or extrahepatic tissues.

The fate of plasma LDL has been elucidated by the work of Brown, Dana, and Goldstein (Goldstein 1973), Goldstein and Brown (1974), and others (Weinstein et al 1976, Bierman et al 1977). LDL binds to specific cell-surface receptors that in fact are B-100/E receptors. These receptors are present on many cell types; however, Dietschy, et al (1983) among others (Carew et al 1982, Kovanen et al 1979) have demonstrated in experimental animals that the liver is the major site of LDL clearance. Circumstantial evidence has been presented by Starzl et al. (Starzl et al 1984), in a hypercholesterolemic child who was genetically devoid of LDL receptors and who underwent liver transplant, that the liver also is the major organ of LDL removal in humans; following transplantation of a normal liver, LDL levels fell to near the normal range. While B-100/E receptors remove most of plasma LDL, a nonreceptor pathway, presumably nonspecific pinocytosis, extracts between 10 and 15% of the circulating LDL pool each day (Bilheimer et al 1979).

Cholesterol metabolism

Cholesterol is a major component of the atherosclerotic plaque, and for this reason, its metabolism has evoked intense interest. The fact that dietary cholesterol can induce atherosclerosis in various animal species lead early workers to speculate that cholesterol in the diet is a major etiological agent in atherogenesis. Although this hypothesis is no longer accepted for human atherosclerosis, excess dietary cholesterol or abnormalities in cholesterol metabolism may contribute in part to atherosclerosis. A review of the basic pathways of cholesterol metabolism thus would seem in order.

Dietary cholesterol and cholesterol absorption. The diet of most Americans contains about 500 mg per day of cholesterol. The absorption of intestinal cholesterol, however, is incomplete and only about 40-60% actually is taken up by the intestinal mucosa (Grundy et al 1977, 1979). Cholesterol is absorbed in the unesterified state; the mucosa esterifies it with oleic acid by the enzyme, acylcholesterolacyl transferase (ACAT). The resulting cholesterol ester becomes incorporated along with triglycerides into chylomicrons. Most of chylomicron cholesterol goes to the liver with chylomicron remnants.

Cholesterol synthesis and catabolism. A normal adult produces 500 to 1000 mg cholesterol daily (8 to 12 mg per kg) (Grundy et al 1979, Bilheimer et al 1979). Somewhat less than half is made in the liver; the remainder comes from a host of other tissues, i.e., the intestine, adrenal, muscle, adipose tissue, skin and other organs (Dietschy et al 1971). Obesity increases the synthesis of cholesterol (Miettinen 1971, Nestel et al 1973). When intake of cholesterol is high, hepatic synthesis of cholesterol falls due to feedback inhibition. Cholesterol synthesis in other tissues however may not be inhibited by newly-absorbed dietary cholesterol.

Cholesterol leaves the body through the liver. Two processes are involved. About one-third to one-half the cholesterol synthesized daily is transformed into bile acids. Both hepatic cholesterol and the bile acids are secreted into bile. They are partially reabsorbed by the intestine. The unabsorbed portion passes into the feces. The intestinal route thus constitutes the major pathway for excretion of cholesterol and its catabolic products.

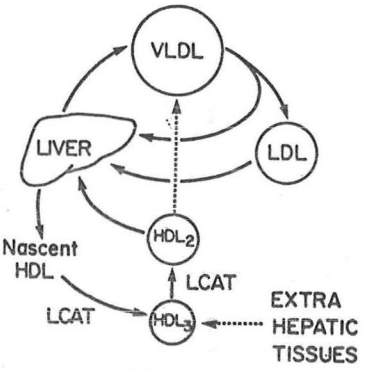
The plasma cholesterol. Cholesterol circulates in plasma bound to the different lipoprotein fractions. For U.S. adults, plasma cholesterol

concentrations range from about 160 to 275 mg/dl (mean 210 mg/dl) (Basu et al 1981). Normally, two thirds of plasma cholesterol is esterified with a fatty acid. The esterification reaction occurs in the plasma by transfer of a molecule of linoleic acid from lecithin to cholesterol. The enzyme responsible for this transfer is lecithin-cholesterol acyltransferase (LCAT). The primary substrate for esterification may be unesterified cholesterol carried on HDL (Grundy 1979). After esterification of HDL-cholesterol, the esters are transferred to VLDL, and to a lesser extent, to LDL.

Reverse cholesterol transport. The mechanism by which cholesterol is removed from tissue is a subject of great interest. The amount of cholesterol in the atherosclerotic plaque depends on the balance between influx and removal. Thus mechanisms for removal of cholesterol from the artery probably could be as important in atherogenesis as those promoting influx.

The entire process of removal of cholesterol from peripheral tissues and return to the liver has been called "reverse cholesterol transport". As shown in Figure 10, cholesterol is released from cells in the unesterified state. Presumably, as the cholesterol content of cells increases it is more easily extracted into extracellular milieu. Recent studies suggest that release of cholesterol from cells is facilitated by cellular production of apo E which is secreted simultaneously with cholesterol (Basu et al 1981). The nature of the "cholesterol acceptor" is unresolved, but many investigators believe that apoproteins A-I and A-II are important (Fielding et al 1982). Another apoprotein, apo D, also has been implicated (Fielding et al 1982). Upon efflux from cells cholesterol is esterified rapidly and incorporated into HDL.

Fig. 10.
-Reverse cholesterol transport
(see test for description of pathways).



All the pathways and fates of cholesterol ester in HDL have not been resolved. A significant portion may be transferred to VLDL, and then to LDL by VLDL catabolism (Fielding et al 1982). The final transfer of cholesterol ester to the liver thus could be mediated through any of the lipoproteins -- VLDL remnants, LDL or HDL.

Plasma lipids, atherosclerosis, and CHD risk.

Total plasma cholesterol. Several large epidemiological studies have shown a positive correlation between total plasma cholesterol and incidence of CHD (Pooling Project 1978, Keys 1970, Grundy et al 1982). This relationship holds for both within-population and cross-population surveys. One important study was the Pooling Project in which several populations in the U.S.A. were surveyed and the data pooled (Pooling Project 1978). The results are summarized in Table 2. In this table risk for CHD is compared to serum cholesterol concentrations through 5 steps (quintiles) of increasing cholesterol levels. The survey included men aged 40 to 64 years. No significant differences were found in CHD rates between quintiles I and II, but risk rose progressively through quintiles III, IV, and V. The relative risk between the quintiles also depended on age. At 45 to 49 years the risk ratio for quintiles IV/I+II was 2.9 and V/I+II was 3.6.

Table 2

Relation Between Cholesterol Levels and CHD Rates (The Pooling Project) (Ages 40-64 years)

Plasma Cholesterol mg/dl	Risk Ratio (CHD events)
<199	1.0
200-219	1.0
220-239	1.15
240-269	1.57
>270	1.92

This and other studies establish a correlation between high plasma cholesterol and coronary atherosclerosis. This correlation however has not been proven to be linear over a broad range of cholesterol levels. A particularly crucial issue is whether the rate of atherogenesis increases linearly with a rising plasma cholesterol concentrations over the whole range of concentrations from low to high. One possibility is that the relationship is curvilinear, so that risk increases with only above a certain "threshold" concentration. The Pooling Project (Pooling Project 1978) in fact does not support a linear relationship; the risk for CHD in the first quintile (plasma cholesterol `194 mg/dl) was not clearly lower than that of the second quintile (195-218 mg/dl). Men with a very low level of cholesterol may have had less CHD, but the data were weak. Carlson (1982) has claimed that the risk for CHD does not increase strikingly until cholesterol levels exceed 250 mg/dl.

This latter conclusion of Carlson (1982) is not necessarily in accord with the world-wide experience in cross cultural surveys. Several studies indicate that peoples in whom cholesterol levels are very low also have a very low incidence of CHD. Notable examples are most populations in the Orient, in Latin America, and in the Middle East (McGill et al 1968, Keys 1970, Grundy et al 1982). Also, the results of the recent MRFIT trial (Stamler et al 1984) provide

some support for a curvilinear relationship between cholesterol levels and CHD mortality, but not necessarily for a threshold relationship. For this study, the risk ratios for CHD mortality were determined for the 361,662 men who were screened. Risk ratios for this group are presented in Table 3. Assuming a baseline level of 182-202 mg/dl for the population screened, people with lower levels had lesser risk, while risk increased progressively above 202 mg/dl. Overall, these results suggest a steeper relationship between CHD and cholesterol level, without evidence of a threshold effect such as that suggested by the smaller number of patients of the Pooling Project.

Table 3

Relation Between Cholesterol Levels and CHD Rates (MRFIT Study)*

Plasma Cholesterol mg/dl	Risk Ratio (CHD Mortality)
<182	0.81
182-202	1.00
203-320	1.30
221-244	1.63
<244	2.50

*361,662 American men of ages 35 to 57 yrs were screened and followed for cause of death; ratios were obtained on 5-yr adjusted mortality rates.

The question of the ideal cholesterol level was addressed specifically by a recent workshop in which a group of epidemiologists, clinical investigators, and experimental pathologists (Stamler 1979). The participants were asked to develop a consensus on what is the ideal cholesterol level. They considered the accumulated data from all sources and concluded that maximum prevention of atherosclerosis should be achieved by adult cholesterol levels in the range of 130 to 190 mg/dl (mean 160 mg/dl).

Plasma triglycerides. Most epidemiological surveys suggest that plasma cholesterol levels are correlated better with rates of CHD than are plasma triglycerides (Hulley et al 1980). Many patients with CHD nevertheless have raised triglyceride levels, and some forms of hypertriglyceridemia may reflect increased risk. There are several different disorders producing hypertriglyceridemia, and the risk associated with each may vary. Thus, a generalization on the relationship between elevated triglycerides and CHD may not be possible; instead, the individual causes of high triglycerides have will to be examined separately, as will be done subsequently.

Individual plasma lipoproteins, atherosclerosis, and CHD risk.

Chylomicrons generally are thought not to be atherogenic. They contain mostly triglycerides which contribute little to plaques. They are relatively large, and presumably filter poorly through the endothelium. Patients with extreme hyperchylomicronemia, due to a congenital deficiency of lipoprotein

lipase, apparently are not prone to premature atherosclerosis (Frederickson et al 1978). Some epidemiological studies also could be taken as an argument against a role of chylomicrons in atherogenesis. For instance, in the Mediterranian region, CHD is rare despite consumption of large quantities of fat (Keys 1970). The dietary fat consumed in this region consists mainly of olive oil; chylomicron formation thus must be normal.

In spite of these arguments, not all investigators agree that chylomicrons are non-atherogenic. Zilversmit (1983) for one suggests that atherosclerosis is largely a postprandial phenomenon. He postulates that chylomicrons interact with endothelial cells on the arterial surface, and during of lipolysis, cholesterol is released and enters the arterial wall. This effect may be more pronounced when the diet is rich in cholesterol. Support for Zilversmit's hypothesis has been obtained by Fielding et al (1978), who reported that triglyceride-rich lipoproteins release of cholesterol during lipolysis in cardiac muscle. Therefore, we cannot say with certainty that chylomicrons are devoid of atherogenic potential, although the evidence is not yet convincing.

Chylomicron remnants. These particles are smaller than chylomicrons, and they have a higher ratio of cholesterol to triglycerides. Theoretically, therefore, chylomicron remnants should be more atherogenic than chylomicrons. In accord, atherosclerosis develops rapidly in cholesterol-fed rabbits which have large quantities of circulating chylomicron remnants (Ross et al 1977). Remnants accumulate in this species because of their slow clearance from plasma. A human counterpart of this animal model is familial dysbetalipoproteinemia, also a remnant-removal disease. In the latter, remnants of both chylomicrons and VLDL accumulate in plasma, and patients have increased atherosclerosis. Whether chylomicron remnants normally resulting from a fatty meal are atherogenic has not been determined.

VLDL. The question of the atherogenecity of VLDL is one of the major unresolved issues in the lipoprotein field. Many patients with coronary heart disease have elevated levels of triglyceride and VLDL (Carlson et al 1972, 1979, Gotto et al 1977). In some cases a high VLDL is the result of a genetic hyperlipidemia; in others it is due to obesity or diabetes mellitus (Grundy 1982). An unusually high percentage of patients with CHD have hypertriglyceridemia (Gotto et al 1977), but some investigators believe that a high VLDL merely reflect other abnormalities in lipoproteins that are the real atherogenic factors (Hulley et al 1980).

Arguments against an atherogenic potential for VLDL are similar to those for chylomicrons. VLDL are relatively large and thus may filter slowly through an intact endothelial barrier. The cholesterol content of VLDL also is low compared to LDL. Some patients clearly have high concentrations of triglycerides for many years without developing of clinical atherosclerotic disease. On the contrary, VLDL under certain circumstances may deliver cholesterol to the arterial wall (Zilversmit 1973). If loss of endothelium is an essential feature of atherogenesis, then VLDL should penetrate the denuded intima. VLDL carry much more cholesterol than chylomicrons; the former therefore should transport more cholesterol into the lesion.

VLDL remnants. These lipoproteins probably are atherogenic. They are smaller than VLDL and are rich in cholesterol (Gofman et al 1950, 1951, 1951, 1954, Borrie 1969, Hessel et al 1976). Plasma concentrations of VLDL remnants

are increased in familial dysbetalipoproteinemia, a disease associated with accelerated atherosclerosis (Borrie 1969, Hessel et al 1976). In cholesterol-fed animals, lipoproteins resembling VLDL remnants accumulate in plasma and generate atherosclerotic lesions (Ross et al 1977). The weight of the evidence thus supports an atherogenic role for VLDL remnants.

LDL are thought to be the most atherogenic species of all the lipoproteins. They are small particles, and extremely rich in cholesterol. Most of the cholesterol in arterial lesions likely is derived from LDL. Marked elevations of plasma LDL, as in familial hypercholesterolemia, predispose to advanced atherosclerosis early in life. Many investigators consider LDL to be etiological factor of great importance in the pathogenesis of atherosclerosis.

Recent work indicates that LDL is not a single species of lipoprotein. It can be divided into subfractions, and the atherogenecity of these fractions may vary. The smallest and heaviest subfraction of LDL may be the most atherogenic, and this possibility needs more investigation.

HDL, in contrast to the lipoproteins discussed above, seemingly is not atherogenic. High levels of HDL actually may protect against atherosclerosis (Krause 1982). If so, protection could be linked to the capacity of HDL to remove cholesterol from tissues. Although a direct protective role for HDL is an intriguing idea, other possibilities must be considered. For instance, high HDL concentrations could reflect an efficient catabolism of VLDL and LDL; when HDL is low, metabolism of VLDL and LDL could be abnormal and associated with a state of heightened susceptibility for atherosclerosis.

Increased production of lipoproteins. It is generally assumed that lipoproteins accelerate atherosclerosis in proportion to their plasma concentrations. Although this may be true, enhanced flux of lipoproteins without hyperlipidemia also may be atherogenic. We have recently reported on a subgroup of patients with early CHD who have increased flux of LDL without hypercholesterolemia (Kesaneimi et al 1983). Several possible reasons for this phenomenon might be considered. First, such patients could have transitory periods of hypercholesterolemia which has not been undetected. Second, an increased flux of LDL may be associated with a more atherogenic species of LDL, as discussed above. Third, overproduction of LDL may "saturate" the normal LDL-receptor pathway leading to increased uptake of LDL by nonreceptor pathways (Goldstein et al 1982); this latter pathway seemingly is involved in development of foam cells. Finally, an enhanced flux of LDL may transport excess cholesterol to peripheral tissues thus overloading of reverse cholesterol transport; this overloading could reduce the exit of cholesterol from the arterial wall.

Genetic hyperlipidemias: Role in atherosclerosis.

Several genetic disorders can produce abnormalities in the plasma lipoproteins. Some but not all of these abnormalities are associated with accelerated atherosclerosis or increased risk for CHD. These conditions also provide useful information about the link between specific lipoproteins. The major forms of genetic hyperlipidemia can be considered.

Primary hyperlipidemia. An elevation of plasma LDL-cholesterol in the absence of hypertriglyceridemia can be called primary hypercholesterolemia. This is synonymous with the phenotypic type 2a hyperlipoproteinemia (HLP). The

term "primary" implies that the elevated plasma cholesterol results from a primary metabolic defect and is not secondary either to other diseases or dietary excesses. Several studies have demonstrated that the most common cause of primary hypercholesterolemia is a defect in the activity of the LDL receptor. The consequences of such a defect is shown in Figure 11. Since circulating LDL is cleared mainly by hepatic LDL receptors, a defect in activity of LDL receptors produces a delayed clearance of plasma LDL by the liver. Likewise, uptake of VLDL remnants by the same receptors is reduced, and as a result, more VLDL is converted to LDL. This simultaneous "overproduction" of LDL and delayed clearance act together to raise LDL levels. A less common cause of hypercholesterolemia is overproduction of VLDL associated with increased conversion of VLDL to LDL. The different causes of primary hypercholesterolemia can be considered.

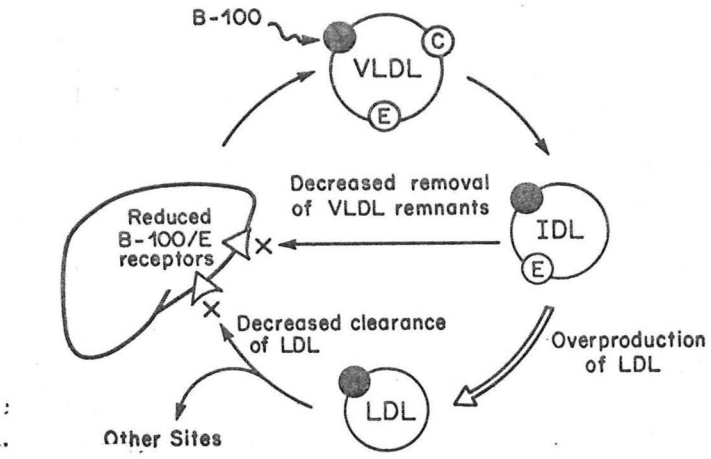


Fig. 11. Effects of a deficiency (or reduction) of apoB-100/E receptors on lipoprotein metabolism. First, hepatic clearance of VLDL remnants (IDL) is reduced, and consequently, more IDL is converted to LDL; and second, clearance of LDL is reduced. The net result is an increase in LDL concentrations.

The most severe form of primary hypercholesterolemia is classical familial hypercholesterolemia. This disorder is caused by a genetic defect in the LDL receptor. One gene for the LDL receptor is inherited from each patent, and in the heterozygous form of familial hypercholesterolemia, the patients have only one normal gene. This reduction in the number of LDL receptors causes severe hypercholesterolemia. The rise in levels of LDL is the result of a reduced fractional clearance of LDL combined with increased conversion of VLDL remnants to LDL (Figure 12). The heterozygous form of this disorder occur in about one in 500 people, and it is characterized by cholesterol levels over 300 mg/dl, tendon xanthomata, and premature CHD. The age of onset of CHD depends on the sex; men frequently develop CHD in the 30's or 40's or even earlier; and in women, the onset often is in the 50's and 60's. Classical familial hypercholesterolemia is a significant cause of premature CHD. Studies by Goldstein et al (1973a, 1973b) suggest that about 10% of patients with premature CHD have this condition. It has been estimated that the risk for CHD in a classical familial hypercholesterolemia is increased from 4-fold to 8-fold over baseline risk.

The metabolic defects responsible for other forms of primary hypercholesterolemia have not been defined. The cholesterol in most patients of

this type are in the range of 250 to 300 mg/dl, and the risk for CHD is increased from 2-fold to 4-fold above baseline. This condition was called "polygenic" hypercholesterolemia by Goldstein et al (1973a,1973b) because it does not follow typical Mendelian inheritance for a monogenic disorder. However, the term "polygenic" is ambiguous because it could mean either that multiple genes conspire in an individual patient to cause hypercholesterolemia, or one individual might have one of several possible genes producing hypercholesterolemia. Several different genetic defects can be visualized whereby cholesterol levels might be raised. One possible cause of primary moderate hypercholesterolemia could be a mild defect in the primary structure of the LDL receptor. Such a defect could impart decrease in receptor affinity for LDL, although it could not cause complete obliteration of binding. One such gene encoding an abnormality in the LDL receptor combined with one normal gene could account for more moderate forms of hypercholesterolemia than found in classical familial hypercholesterolemia. Another metabolic defect could be an abnormality in the regulation of synthesis of LDL receptors. The production of receptors is under complex biochemical control, and it is linked in some way to the activity of cholesterol biosynthesis. A defect in these control mechanisms might produce a sluggish synthesis of LDL receptors. Finally, an abnormality might lie not in the receptor, but in LDL itself. For instance, an abnormality in the primary structure of apolipoprotein B could render LDL a poor ligand for the receptor; a diminished binding of LDL for its receptor again could result in moderate hypercholesterolemia.

The incidence of these other forms of primary hypercholesterolemia is unknown. In some patients with cholesterol levels in the range of 250 to 300 mg/dl, the ingestion of hypercholesterolemic foods is a confounding variable. One the other hand, many people have desirable levels of cholesterol despite dietary excesses, and we therefore might ask whether any patient who has a cholesterol level above 250 mg/dl does not have some type of genetic abnormality. If so, the prevalence of primary hypercholesterol other than classical FH is high; approximately 15% of the adult American population has cholesterol levels over 250 mg/dl, and it is from this population that a large portion of all CHD is derived.

Remnant removal defects

An important advance in recent years is the recognition that apo E plays a crucial role in the removal of remnants of TG-rich lipoproteins. The chylomicron remnant receptor may recognize apo E, whether it is on remnants of chylomicrons or large VLDL. Apo E also appears to promote removal of smaller VLDL remnants via the LDL receptor. There are three major isoforms of apo E including E-3, E-4, and E-2 (Zannis et al 1982), and all isoforms do not have the same affinity for receptors. Apo E-3 binds tightest to the receptor, E-4 next, and E-2 least. Every person inherits two genes for apo E and thus 6 genotypes are possible: E-3/3, E-3/4, E-3/2, E-4/4, E-4/2, and E-2/2. People with the E-2/2 genotype tend to accumulate remnants because of sluggish removal. In the absence of other defects in lipoprotein metabolism, however, the E-2/2 pattern rarely causes frank hyperlipidemia, i.e., it remains a latent defect (Utermann et al 1980).

Defects in Lipolysis

Two factors can be responsible for defective lipolysis of plasma TG--a reduction in the availability of LPL and an abnormality in the lipoproteins themselves rendering them a poor substrate for the enzyme. With regard to the former, rare patients have a congenital absence of LPL (Nikkila 1983). Such patients, who are homozygous for LPL deficiency, have marked elevations of TG-rich lipoproteins, especially chylomicrons. VLDL levels generally are not increased proportionately. This pattern of high chylomicron levels and normal VLDL is called type 1 hyperlipoproteinemia (HLP). Why are VLDL levels not increased in proportion to chylomicrons? There are two possibilities: first, the synthesis of VLDL likely is relatively low in most type 1 patients; but perhaps more important, many newly secreted VLDL may be the size of chylomicra and thus are mistakenly called chylomicrons. The finding that the chylomicron fraction of patients with defective lipolysis contains appreciable quantities of apo B-100 is compatible with the hepatic secretion of some very large VLDL (Stalenhoef et al 1984).

If complete deficiency of LPL results in severe chylomicronemia, are there partial deficiencies responsible for milder hypertriglyceridemia? Of interest, heterozygotes for LPL deficiency usually have normal plasma TG levels, although they may have a mild clearance defect for chylomicrons (Harlan et al 1967). Several reports nonetheless claim that some patients with elevated plasma TG have abnormalities in LPL--either quantitative or qualitative (Huttunen et al 1976, Goldberg et al 1980, and Beil et al 1982). These reports are highly suggestive that reduced activity of LPL can raise plasma TG, but the existence of definitive abnormalities in LPL function is difficult to prove in the intact patient. A portion of hypertriglyceridemic patients apparently have a reduction in heparin-releasable LPL, while others have a decrease in LPL in adipose tissue. Unfortunately, it is difficult to relate these defects to changes in the in vivo activity of LPL, and more studies are needed to determine to what extent abnormalities in the metabolism of LPL, without complete absence of the enzyme, contribute to hypertriglyceridemia.

Another cause of hypertriglyceridemia can be a defect in composition of apoproteins of TG-rich lipoproteins. This cause is best illustrated by patients who have a congential absence of apo C-II (Breckenridge et al 1978), the apoprotein required for activation of LPL (LaRosa et al 1970). In this condition, marked hypertriglyceridemia occurs. It has been suggested that a partial deficiency of apo C-II likewise can raise TG levels (Carlson et al 1976, Catapano 1980, Kashyap et al 1977), but this mechanism for hypertriglyceridemia is questionable. Nor has it been shown that abnormalities in other apoproteins, such as apo C-III or apo E, affect the interaction of lipoproteins with LPL in vivo. The size of TG-rich particles could be another important factor determining lipolytic rates. Chylomicrons seemingly are much better substrates for LPL than are the smaller VLDL. Within the VLDL fraction, size too may be important. Large VLDL may undergo rapid lipolysis and be cleared quickly from the circulation, possibly by chylomicron remnant receptors (Stalenhoef et al 1984). The TG of smaller VLDL apparently is hydrolyzed less rapidly. Consequently, if there is an increased input of small VLDL, sluggish lipolysis of their TG could raise TG levels.

Overproduction of lipoproteins

There is increasing evidence that overproduction of lipoproteins, particularly of VLDL, contributes significantly to several forms of hyperlipidemia. This evidence has been forthcoming from isotope kinetic studies that trace the input and exit of apo B-containing lipoproteins. Since the number of apo B molecules per lipoprotein particle is constant (Shumaker et al 1984), quantification of apo B kinetics should accurately follow the metabolism of lipoprotein particles.

Increased secretion of VLDL can be either primary or secondary. The causes of primary lipoprotein overproduction are unknown. Whether excessive synthesis of apo B without a concomitant overproduction of VLDL-TG can lead to increased secretion of VLDL particles remains to be determined. Causes of secondary lipoprotein overproduction are obesity with a high caloric intake (Kissebah et al 1981, Kesaniemi et al 1983), diabetes mellitus (Kissebah et al 1983), and probably the nephrotic syndrome. High carbohydrate diets and excess alcohol intake can stimulate synthesis of VLDL-TG (Melish et al 1980, Crouse et al 1984), but these stimuli may merely expand the size of VLDL particles with extra TG and not increase the number of particles secreted (Melish et al 1980).

Overproduction of VLDL seemingly is associated with a high absolute conversion of VLDL to LDL, i.e. it causes overproduction of LDL (Kesaniemi et al 1983, Kissebah et al 1983). Theoretically, hypersecretion of VLDL might raise levels of both VLDL and LDL. Overproduction of VLDL however does not always induce hyperlipidemia (Figure 12A). Lipoprotein overproduction without hyperlipidemia has been reported in obese patients (Kesaniemi et al 1983a), in patients with adult-onset diabetes (Kissebah et al 1983), and in some patients with premature coronary heart disease (Kesaniemi et al 1983b). Protection from development of hyperlipidemia in overproducers appears to be afforded by a compensatory increase in clearance rates of lipoproteins. For example, most patients who have overproduction of VLDL and increased absolute conversion of VLDL to LDL also have enhanced clearance rates of LDL (Vega et al 1985). The reason for accelerated clearance of LDL is unclear. In overproducers of VLDL, LDL frequently are "polydisperse" or heterogenous in size (Vega et al 1985, Fisher 1983). Some of these particles could have an unusually high affinity for the LDL receptor.

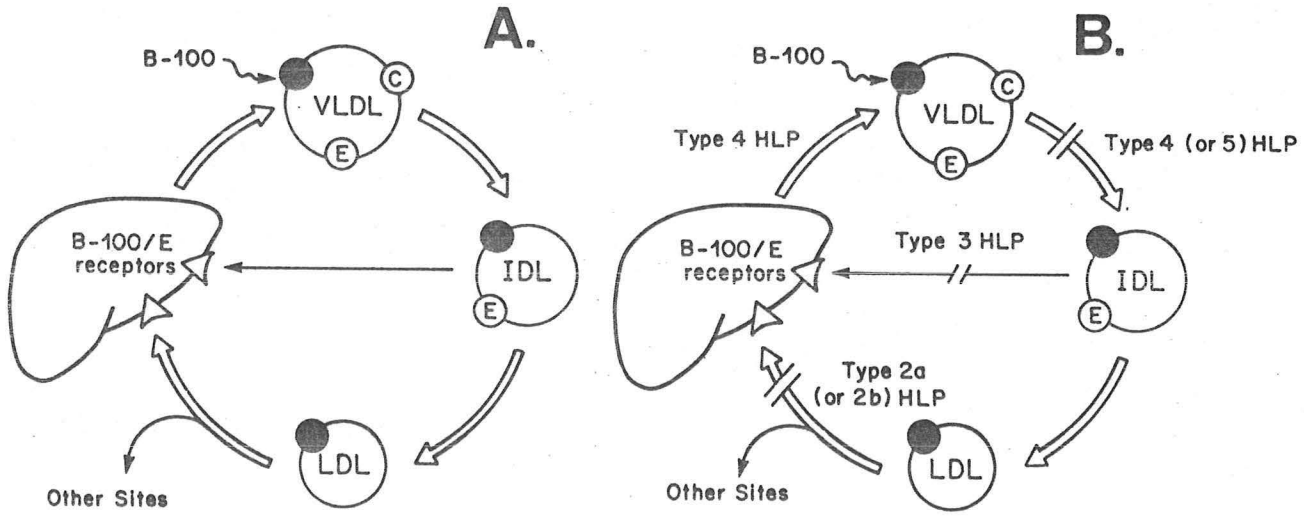


Fig. 12. Metabolic consequences of overproduction of VLDL. A. Some patients have overproduction of VLDL without developing hyperlipidemia. They have a high flux rate of VLDL, IDL, and LDL but, because of efficient clearance mechanisms, the concentrations of these lipoproteins are not increased. B. Other patients with overproduction have defective clearance of one or more lipoproteins. Simultaneous overproduction of VLDL-apoB and VLDL-TG can cause type 4 HLP. Defective lipolysis can yield either types 4 or 5 HLP. The E-2/2 genotype delays clearance of VLDL remnants causing type 3 HLP. Finally, a defective clearance of LDL can produce either hyperapobetali-

On the other hand, many patients with VLDL overproduction do in fact have hyperlipidemia. If overproduction of VLDL-apo B is associated with excessive synthesis of VLDL-TG the result will be endogenous hypertriglyceridemia, or type 4 HLP (Beil et al 1982). However, in most instances in which hyperlipidemia is associated with overproduction of VLDL, there seemingly is a concomitant defect in clearance of one or another lipoprotein species (Figure 12B). For example, the type 4 phenotype also can be the result of the combination of overproduction of VLDL and a lipolytic defect for plasma TG (Beil et al 1982). The latter may be mild, i.e. a latent defect, so that hypertriglyceridemia would not be present in absence of overproduction. When the lipolytic defect is more severe, in both VLDL and chylomicrons will be elevated (type 5 HLP). We have shown recently that type 5 HLP usually is the result of a dual defect in TG metabolism--defective clearance of TG-rich lipoproteins plus overproduction of VLDL-TG (Kesaniemi et al 1984). The latter abnormality can be primary or secondary; indeed many type 5 patients have either diabetes mellitus or obesity (or both) as causes of their overproduction.

When hypersecretion of VLDL is combined with the apo E-2/2 genotype, a marked increase in VLDL remnants, or beta-VLDL, occurs (Berman et al 1978); this pattern, which is called type 3 HLP, is a good example of how a latent catabolic defect can accentuate hyperlipidemia in a patient with overproduction of VLDL. Without overproduction, the E-2/2 genotype imparts only trivial increments in remnant lipoproteins, but when input of VLDL is excessive, remnants accumulate to a striking degree.

Finally a high secretion of VLDL can cause elevated levels of LDL. Usually however LDL levels do not rise to abnormally high levels despite enhanced conversion of VLDL to LDL. As mentioned before, the LDL particles associated with overproduction of VLDL are abnormal, and they tend to be cleared rapidly from the circulation. On the other hand, if secretion of VLDL is extremely high, causing massive conversion of VLDL to LDL, the plasma LDL will be elevated (Vega et al 1985). Furthermore if a concomitant defect in clearance of LDL is present, LDL levels also will be high. An elevated LDL can occur in two forms--hyperapobetalipoproteinemia and type 2 HLP. Hyperapobetalipoproteinemia was defined by Sniderman et al (1980, 1982) as an increase in LDL-apo B levels with a normal plasma LDL-C. This relationship can exist because the apo B-to-cholesterol ratio in LDL is abnormally high in the presence of VLDL hypersecretion. A rise in the number of LDL particles LDL therefore will cause an abnormally high level of LDL-apo B while LDL-cholesterol remains in the normal range. Thus, hyperapobetalipoproteinemia usually is the result of a mild defect in clearance of LDL linked with overproduction of VLDL. A more severe defect in LDL clearance leads to elevations in LDL-cholesterol as well as in LDL-apo B and hence to type 2 HLP.

The combination of overproduction of VLDL and one or more catabolic defects for various lipoprotein species explains how multiple lipoprotein phenotypes can occur within a single family. This phenomenon was designated <u>familial combined hyperlipidemia</u> by Goldstein et al (1973a,1973b), and families with this condition were noted to have a variety of lipoprotein abnormalities--types 2a, 2b, 4, and 5 HLP. Since this first description, additional variants have been recognized to belong to the lipoprotein overproduction disorder, namely, type 3 HLP (Berman et al 1978), hyperapobetalipoproteinemia (Sniderman et al 1980, 1982), and a normolipidemic variant (Kesaniemi 1983b, Vega et al 1985, Vega et al 1983). Furthermore, these multiple variants can occur whether the overproduc-

tion is on a primary or secondary basis. One of the challenges for future study of this disorder is to understand the molecular basis for overproduction of apo B-100 lipoproteins by the liver.

Hypoalphalipoproteinemia (Low HDL)

Considerable evidence points to a low plasma HDL (hypoalphalipoproteinemia) as a significant predictor of CHD in high risk cultures. The risk ratios for HDL-cholesterol as related to CHD obtained in the Framingham Heart Study (Castelli et al 1977, Gordon et al 1977) are presented in Table 4. This latter table shows the relative risk for developing CHD at various concentrations of HDL-cholesterol compared to the mean levels for men (45 mg/dl) and for women (55 mg/dl). These ratios appear to be applicable over a broad range of HDL-C levels.

Table 4

Relative Risk for CHD at Different Plasma Levels of HDL-C

Plasma HDL-C mg/dl	Risk Ratio Men	Women
30	1.82	-
35	1.49	-
40	1.22	1.94
45	1.00	1.55
50	0.82	1.25
55	0.67	1.00
60	0.55	0.80
65	0.45	0.64
70	-	0.52

Evidence that HDL levels contribute to the development of atherosclerosis comes from two other sources. For example, in the Oslo Autopsy Study (Solberg et al 1980) there was a significant inverse relationship between HDL-cholesterol and extent of atherosclerosis in the coronary arteries. Also, a similar inverse relation has been reported for the extent of coronary artery disease as determined by coronary angiography (Miller et al 1981, Whayne et al 1981, Swanson et al 1981, Holmes et al 1981, Maciejko et al 1983).

Diet and coronary heart disease

Few questions have generated such heated debate as the "Diet-Heart" issue. One of the reasons is that the issue is complex, and there are no simple answers. First, the diet contains many substances, and these different substances could affect atherogenesis differently. And second, the various nutrients could act through more than one mechanism. In this review, we will examine the various nutrients for their possible actions on atherosclerosis and on the risk for CHD.

Dietary cholesterol. Since early studies showing that feeding of dietary cholesterol to experimental animals induces atherosclerosis, many investigators

have believed that excess dietary cholesterol must be an important atherogenic factor in man. Several studies have shown that increasing dietary cholesterol can raise levels of plasma cholesterol and LDL in man (Beveridge et al 1959, 1960, Connor et al 1961, 1961, 1974, Keys et al 1950, 1965, Mattson et al 1972, Mahley 1982, Rudel et al 1977, Grundy 1961). The current U.S. diet contains approximately 500 mg of cholesterol per day. This amount, above a zero cholesterol intake, should raise plasma total cholesterol by as much as 35 mg/dl (Keys et al 1950, 1965, Mattson et al 1972). An increase of this magnitude in turn should produce a finite increment in risk for CHD, and would qualify dietary cholesterol as an important secondary risk factor.

As characteristic of other secondary risk factors, the response in plasma cholesterol to dietary cholesterol varies from person to person. Studies in experimental animals confirm this variability. Even within a single species, especially for nonhuman primates, some animals demonstrate a marked rise in plasma cholesterol when cholesterol is fed. Others in contrast show only mild increases. For this reason, the notion has been put forward that some people are "responders" and others are "nonresponders" to dietary cholesterol. The extent to which this concept can be applied to humans remains to be resolved. Some variability in response clearly exists. Differences in response however are not as marked as can occur in nonhuman primates, nor is dietary cholesterol likely to be as atherogenic in man as in these species.

An intriguing idea is that dietary cholesterol may promote atherogenesis by mechanisms other than by raising plasma LDL. One possibility is that dietary cholesterol carried in chylomicrons or chylomicron remnants can find its way into the arterial wall, as suggested by Zilversmit (Keys et al 1950, 1965, 1965, Mattson et al 1972). Another is induction of unusually atherogenic lipoproteins by cholesterol in the diet; two prominent examples in experimental animals are the formation of highly atherogenic β-VLDL (Mahley 1982) and large LDL (Rudel et al 1977). Still another possibility is a decrease in hepatic receptors for LDL following uptake of large amounts of chylomicron cholesterol by the liver. If this latter response occurs, LDL might be diverted to extrahepatic tissues for clearance, a process that could accelerate atherosclerosis. If any of these mechanisms pertain, they could occur without raising levels of fasting total cholesterol or LDL. Dietary cholesterol nevertheless would still be classified a secondary risk factor, but effects on atherogenesis could be unique to cholesterol absorbed through the intestinal tract.

Saturated fatty acids.

The other major dietary constituent raising plasma cholesterol is fat containing saturated fatty acids, particularly palmitic acid. Evidence that these fatty acids are a risk factor has been reviewed recently (Grundy 1961). For every one percent of total calories contributed by these fatty acids the plasma cholesterol increases by an average of 2.7 mg/dl. Again however the response is variable from one person to another. Some people are able to maintain LDL levels in the desirable range despite ingestion of large amounts of saturated fats. Others have mild increases but into a range where risk for CHD is enhanced. And still others have a marked response which may greatly raise their risk. If saturated fatty acids affect risk for CHD in any way other than increasing LDL levels, it has not been uncovered. The mechanism by which these fatty acids raise plasma LDL has not been resolved. They probably decrease clearance of LDL from the circulation, but increased production of LDL is another possibility.

HYPERTENSION

Hypertension as a risk factor

Established hypertension. Sustained hypertension is responsible for numerous cardiovascular complications including cerebral hemorrhage, cardiomegaly, heart failure, and renal failure; on a population-wide basis, however, the major consequence of hypertension is occlusive vascular disease. Several epidemiological studies have shown that sustained hypertension, with blood pressure readings over 140/90 mm Hg, is a major risk factor. One of these surveys was the Framingham Study (Dawber 1980). In this study, incidence of CHD was three to five times greater in patients with established hypertension than in those with normal blood pressure. Risk was enhanced in patients who had either systolic or diastolic hypertension, although the two usually went together. The increased risk from hypertension extended to all vascular beds (coronary, cerebral, and peripheral). Other epidemiological studies, such as the National Cooperative Pooling Project, (Pooling Project 1978) have claimed a similar relation between established hypertension and CHD risk. Table 5 presents risk ratios for developing CHD as determined for 8,381 men, ages 40-64, in the Pooling Project.

Table 5

Risk Ratios for CHD at Various Readings of Diastolic Blood Pressure (8,381 Men; Ages 40-64)

Diastolic Blood Pressure	Risk Ratio
mmHG	
<80	1.00
80-88	1.42
89-94	1.60
>94	2.29

Borderline (mild) hypertension as risk factor. "Borderline (mild) hypertension" apparently is associated with increased risk for cardiovascular disease. For present purposes mild hypertension can be defined as the lowest blood pressure that imparts increased risk for clinical atherosclerotic disease without significantly enhancing danger of other hypertensive complications (e.g., heart failure, renal disease, or cerebral hemorrhage). Using these criteria, the upper limit of ideal diastolic pressure may be as low as 75 mm Hg, and for systolic pressure, it may be as low as 110 mm Hg (Dawber 1980). Criteria such as these are not necessarily universal. For instance, slightly-elevated blood pressures may enhance risk for CHD more in U.S. men, who are at greater risk from other factors, than in U.S. women or other populations at otherwise low risk.

The magnitude of the increase in risk for CHD associated with mild hypertension is difficult to assess because of differences in criteria and population selections, but available evidence for Western men still suggests that it is substantial. For example, in the National Cooperative Pooling Project, (Pooling

Project 1978) men with diastolic pressures in the range of 85 to 94 had almost twice the risk for CHD as those whose diastolic pressure was below 75 mm Hg (Table 5). From all the available data a fairly good generalization is that a blood pressure of 140/90 mm Hg in U.S. men essentially doubles the risk for CHD as compared to a reading of 120/80 mm Hg.

Hypertension and documented atherosclerosis.

Not only is high blood pressure a clinical risk factor for occlusive vascular disease, antecedent hypertension definitely increases the severity of atherosclerosis found. This relationship has been demonstrated in several pathological studies (McGill et al 1968, Sternby 1968, Strong et al 1972); in the International Atherosclerosis Project the effects of hypertension on atherosclerosis were noted at all sites understudy (e.g., Oslo, New Orleans, Jamaica, Santiago, and Guatemala) regardless of the average severity of atherosclerosis (McGill et al 1968) The association between hypertension and atherosclerosis is related more closely to fibrous plaques than to fatty streaks (McGill et al 1968), although this may be true of all the major risk factors. Hypertension has been shown to enhance development of atherosclerosis in both the aorta and coronary arteries (Table 6).

Table 6

Association between Hypertension and Degree of Atherosclerosis Determined for Coronary Arteries and Aorta*

Study	Coronary	Aortic
Intern. Ath. Project	++	++
New Orleans	++	++
Malmo	++	++
Puerto Rico	++	++
Honolulu	-	+
Framingham	-/+(M/F)	NA

* (+) means positive correlation; (++) indicates strong association; (-) signifies no association; NA means not available, and (M/F) refers to male/female.

Despite the impact of hypertension on the development of atherogenesis, an elevated blood pressure in the absence of other significant risk factors may not produce enough occlusive disease to cause the frequent occurrence of clinical CHD. For instance, hypertension is common in Jamaica, but CHD is rare (McGill et al 1968). Thus, hypertension appears to have a strong interaction with other risk factors, particularly hypercholesterolemia, in the causation of CHD.

Hypertension and mechanisms of atherosclerosis.

Although hypertension is a major risk factor for CHD, little research has gone into studying mechanisms by which it accelerates atherosclerosis. The data and hypotheses currently available can be reviewed.

Hemodynamic factors. The most widely accepted hypothesis is that hypertension accelerates atherosclerosis by damaging the arterial wall. Through this "damage" it sets into motion a train of events leading to growth of atherosclerotic plaques. The possible hemodynamic consequences of hypertension have been reviewed thoroughly by Glagov (Glagov 1972). Atherosclerosis has a predilection for certain sites in the arterial tree. Lesion formation is common at sites exposed to abnormalities in flow or tension characterized by (a) turbulence (departures from laminar flow), (b) boundary conditions related to different rates of laminar flow, and (c) changes in wall pressures.

The bruit heard over an atherosclerotic plaque dramatic illustration of turbulance of flow; undoubtedly, lesser and inaudible instances of turbulance occur at sites of curvature or narrowing. Disturbances in patterns of flow may induce changes in the arterial intima, especially loss of the endothelial barrier. Vibrations set up in the arterial wall cause hypertrophy of the media as seen around arteriovenous fistulas (Solberg et al 1970). Whether vibrations also lead to intimal changes is not clear.

Even the normal flow of blood through an artery produces a shearing force on the surface, and may cause a deformation of the endothelial lining. Increased rates of flow are seen normally at branches and bends in arteries. Several different effects have been postulated. One is a "suction" action that would lift up the intimal surface (Solberg et al 1970). Another is fibromuscular hyperplasia in response to local turbulence of blood. Fry (Fry 1973) has shown that local turbulence indeed does cause areas of injury and erosion. Although most investigators believe that atherosclerosis is greatest where sheer stress is highest, Caro et al. (Caro 1969), contend that lesions are most likely to occur in zones where drag is least and boundary layer are thick allowing for more transintimal infiltration of lipids.

While turbulence and sheer forces appear to be increased with hypertension, and may promote atherogenesis by damage to the intimal surface, tangential pressure clearly is greater when blood pressure is high. One effect of a high tangential pressure may be to enhance filtration of plasma lipids through the intima. Increased pressure alone however does not necessarily promote transendothelial flux of lipoproteins; this is because movement of lipoproteins through the endothelium may depend more on vesicular transport than on diffusion through intercellular spaces. Still, multiple alterations induced by hypertension may work in concert to promote filtration of lipoproteins into the arterial wall. For example, turbulence and sheer forces may disrupt the endothelial barrier to lipoprotein influx, while greater tangential pressure should force more lipoproteins into the arterial wall.

SMOKING

Smoking as a risk factor.

For the past 20 years it has been known that smoking is associated with increased cardiovascular mortality. Cigarette smoking has been positively correlated with the occurrence of myocardial infarction and death from CHD (Glagov 1972, Pooling Project 1978, Kahn 1966, Hammond et al 1969). Tobacco use also is related to development of peripheral vascular disease (Glagov 1972).

Data relating cigarette smoking to relative risk for CHD death by age, sex, and number of cigarettes per day are presented in Table 7. For both men and women, the ratios are highest at the youngest ages. This testifies to the need to stop the smoking habit as early in life as possible. The potential value to the patient of stopping smoking is illustrated by the data shown in Table 8. These data indicate that benefit by reduced risk beings after as short a time as one year after smoking cessation and after several years, the risk returns almost to baseline.

Table 7

Cigarette Smoking and Relative Risk of CHD Death in 6 years
by Age, Sex, and Number of Cigarettes per Day
American Cancer Society Study, 1969

358,534 Men

Cigarettes per day	Relative Risk of CHD Death, by Age				
	40-49	50-59	60-69	70-79	40-79*
Nonsmoker	1.00	1.00	1.00	1.00	1.00
1-9	1.60	1.59	1.48	1.14	1.45
10-19	2.59	2.13	1.82	1.41	1.99
20-39	3.76	2.40	1.91	1.49	2.39
40 +	5.51	2.79	1.79	1.47	2.89

445,875 Women

Nonsmoker	1.00	1.00	1.00	1.00	1.00
1-9	1.31	1.15	1.04	0.76	1.07
10-19	2.08	2.37	1.79	0.98	1.81
20-39	3.62**	2.68	2.08**	1.27	2.41**
40 +	33.1	3.73	2.02	--	3.02

* Unweighted average of relative risks for four age groups, 40-49, 50-59, 60-69, 70-79

** Based on only 5-9 deaths

*** Unweighted average of relative risks for three age groups, 40-49, 50-59, 60-69

Table 8

Lower CHD Risk of Male Ex-Smokers, Compared to Current Smokers Number of Cigarettes Formerly Smoked and By Years since Stopping, American Cancer Society Study, 1969 (276)

Cigarette Smoking Status at Entry	Relative Risk of CHD Death*	
	Smokers of 1-9 Cigarettes Per Day	Smokers of 20+ Cigarettes Per Day
Current Smoker	1.90	2.55
Stopped less than 1 year	1.62	1.61
Stopped 1-4 years	1.22	1.51
Stopped 5-9 years	1.26	1.16
Stopped 10-19 years	0.96	1.25
Stopped 20+ years	1.08	1.05
All Ex-Cigarette Smokers	1.16	1.28

*Relative risk compared to age-matched men who had never smoked regularly.

The relation of smoking to the degree of atherosclerosis has been a subject of some controversy. Several early studies have indicated that smoking is associated with increased atherosclerosis at autopsy (Wilens et al 1962, Auerbach et al 1965, Sackett et al 1968, and Strong et al 1969, 1976). However, data from more recent studies have been less consistent, and the severity of arteries and the aorta. This discrepancy is shown in Table 9. Most studies have shown that the degree of atherosclerosis is worse in the aorta than in the coronary arteries.

Table 9

Association between Smoking and Degree of Atherosclerosis Determined for Coronary Arteries and Aorta*

Study	Coronary	Aortic
East Orange VA	++	NA
New Orleans	+	++
Oslo	-	++
Malmo	-	++
Puerto Rico	-	+
Honolulu	+	+
Framingham	-	NA
Average	±	++

* (+) means positive correlation; (++) indicates strong association; (-) signifies no association; and NA means data not available.

In one earlier study carried out at the Veterans Administration Hospital of East Orange, N.J. (Auerbach et al 1965), vascular changes in the coronary arteries were compared to smoking and age in 1,056 men. This study showed a very high correlation between smoking and percentage distribution of patients with moderate and advanced atherosclerosis (Figure 13). A microscopic examination of the lesions noted that fibrous thicking of the intima was more frequent and more advanced in smokers. Marked hyaline thicking of the myocardial arterioles also was found in 91% of these smoking two or more packs of cigarettes per day, and it never occurred in nonsmokers. An interesting finding was that exsmokers had less atherosclerosis than those patients who were smokers at time of death.

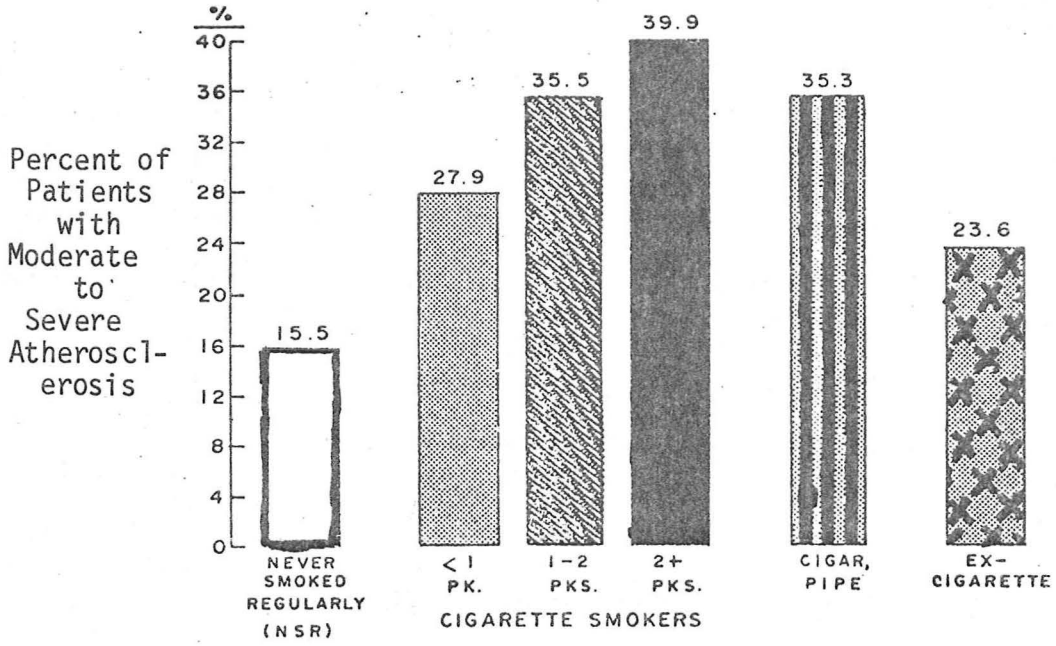


Fig. 13. Distribution by percentage of moderate and advanced atherosclerosis by smoking habit. (from Auerbach et al, 1976)

Another important study was that of Strong and Richards (1976) in which smoking was correlated with atherosclerosis at autopsy in 1320 men ages 25-64. Heavy smokers had about 50% more coronary atherosclerosis and 100% more disease in the abdominal aorta than nonsmokers. The increase in atherosclerosis was mainly in fibrous plaques and not in fatty streaks. Tracy et al (1981) have postulated that smoking enhances rates of conversion of fatty streaks to fibrous plaques, but has little effect on formation of fatty streaks.

As shown in Table 9, all the studies found a relationship between the degree of aortic atherosclerosis and smoking. On the other hand, the prospective autopsy studies of Oslo, Malmo, Puerto Rico, and Framingham did not yield a relation between coronary atherosclerosis. The Oslo study however did report a

relation of smoking with cerebral atherosclerosis, and the Malmo study noted an association with atherosclerosis in both cerebral and peripheral arteries.

The failure to find a relation between coronary atherosclerosis and smoking is difficult to explain. The problem may be methodologic, because despite a large population base in the prospective studies, the number of cases actually autopsied was relatively small. Another possibility however must be considered. Smoking may raise the risk for CHD in ways other than by accelerating the development of atherosclerosis. For example, it could promote the formation of coronary thrombosis on preexisting plaques, or it might precipitate fatal arrhythmias in patients with mild to moderate coronary lesions. The rapid fall off in risk found in exsmokers is consistent with these concepts. A final intriguing possibility is that atherosclerotic plaques may actually regress in patients who quit smoking.

The relation between smoking and CHD raises another interesting question about the significance of risk factors in general. This question arises from data such as those shown in Figure 14. This figure plots the number of cigarettes per day during the last 10 years of life with the percent of the intimal surface of coronary arteries covered with raised lesions as determined by autopsy. Results from this study in New Orleans (Strong 1977) gives results for both whites and blacks. For both races, smokers had a more atherosclerosis on the average, perhaps about two fold higher, than did nonsmokers. However, small amounts of atherosclerosis do not lead to CHD, and it has been estimated that the risk for CHD does not increase substantially until at least 50% of the intimal surface is covered with lesions. If this is true, the cases with a "critical" level of atherosclerosis was almost all smokers. Very few nonsmokers had more than 50% coverage with raised lesions. Thus the risk for CHD would appear to be much higher in some smokers than in all nonsmokers. Indeed, these data suggest that CHD will occur almost exclusively in smokers. This possibility may well be true as suggested by the high rates of smoking in patients who actually do develop CHD. For example, in the Coronary Artery Surgery Study (CASS), which avoided elderly patients, about 85 per cent of all patients entering the study were either smokers or exsmokers. This fact seems to support our interpretation of the data in Figure 14. Also, it suggests that smoking may be the most important single risk factor for CHD.

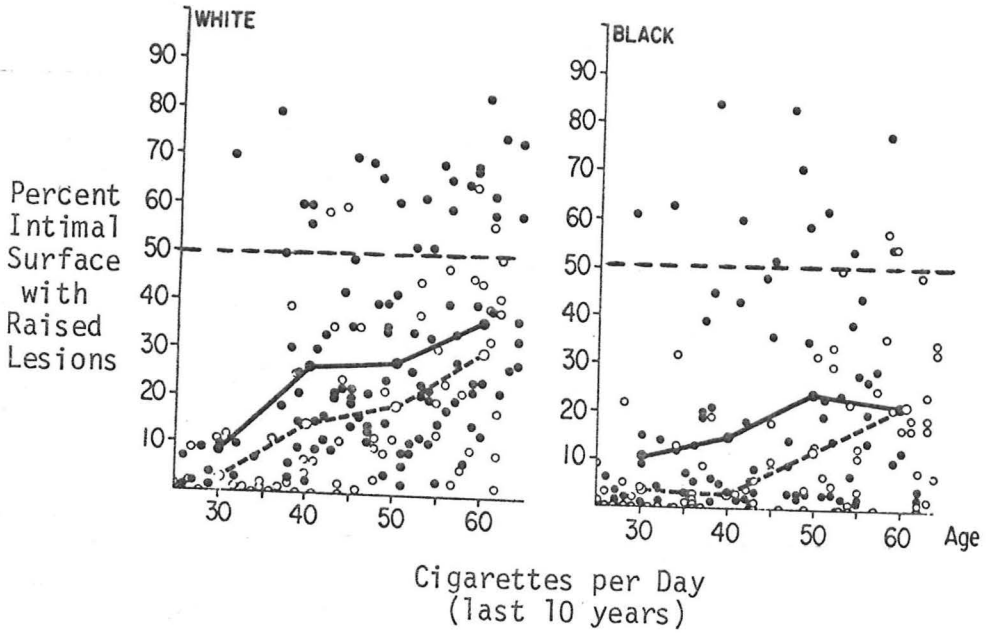


Fig. 14. Percentage of intimal surface of coronary involved with raised lesions by age and average rate of smoking last 10 years of life, basal groups of whitle nonsmokers and heavy smokers and block nonsmokers and heavy smokers.

The risk for cardiovascular death in heavy smokers is approximately twice that to nonsmokers. Thus, while smoking has serious effects on other diseases--chronic bronchitis, emphysema, lung cancer, and other cancers--the most serious and widespread consequence of cigarette smoking is premature CHD.

Atherogenic mechanisms for smoking.

The way in which smoking accelerates atherosclerosis is completely unknown. Cigarette smoke contains many substances; some of these may affect atherogenesis. Also, smoking itself has several physiological actions that could promote atherosclerosis. Although little attention has been given to pathogenetic mechanisms linking smoking and atherosclerosis, their potential importance should not be overlooked. If these mechanisms could be defined, they might be prevented. Several possible or postulated mechanisms thus can be reviewed briefly.

Nicotine. One of the major constituents of tobacco smoke is nicotine, and nicotine might accelerate atherosclerosis (Wenzel et al 1959, Stefanovich et al 1969, Schievelbein et al 1970, Fisher et al 1973). In experimental animals however administration of pure nicotine generally does not induce or increase atherosclerosis. Some thus have concluded that the atherogenic effect of smoking is unrelated to nicotine. This conclusion may be premature. Nicotine stimulates the sympathetic nervous system and can cause vasoconstriction, tachycardia, and a sometimes rise in blood pressure. Cigarette smoking therefore may induce transient hypertension in some patients. Since high blood pressure is a well-established primary risk factor, nicotine in tobacco smoke at the very least can be called a secondary risk factor in those patients who show a hypertensive response. The importance of pure nicotine in human atherogenesis nevertheless remains to be determined.

Carbon monoxide. Smoking increases the carbon monoxide content of blood. A statistical association has been reported between atherosclerotic disease and levels of carboxyhemoglobin in tobacco smokers (Wald et al 1973). Administration of pure carbon monoxide also accelerates atherogenesis in cholesterol-fed animals (Astrup et al 1970, Webster et al 1968, Armitage et al 1976, Sarma et al 1975). The way in which carbon monoxide promotes atherosclerosis is obscure: it could increase capillary permeability, stimulate proliferation of arterial smooth muscle cells (possibly by causing a mild hypoxia), or affect the processing of cholesterol by cells of the arterial wall.

Cadmium. Cigarette smoke contains cadmium, and smoking increases body stores of cadmium. In one study a correlation was found between the cadmium/zinc ratio in the kidney and degree of atherosclerosis (Voors et al 1975).

Smoking and lipoproteins. Cigarette smoking seemingly does not alter the plasma lipoproteins markedly, but small effects can occur. Perhaps the most consistent is a reduction in concentrations of HDL (Voors et al 1975, Hulley et al 1977, Criqui et al Phillips et al 1981). A higher level of VLDL also has been reported for smokers, (Phillips et al 1981) but LDL concentrations seemingly are not affected significantly. To the extent that smoking raises VLDL and lowers HDL it can be called a secondary risk factor.

Epidemiological data suggest that the atherogenic potential of smoking is a function of plasma lipoprotein concentrations. In populations whose total plasma cholesterol is below 180 mg/dl, the incidence of CHD is low (Keys 1970) even when smoking is common. This observation is consistent with the concept that lipoproteins are the more direct atherogenic agent, while the actions of smoking are supportive.

Effects of smoking on other processes in atherogenesis. Smoking exposes the body to myrid of foreign chemicals, and the possibility must be considered that some of these promote atherogenesis. The products of tobacco smoke could damage endothelium, promote formation of platelet thrombi, stimulate proliferation of arterial smooth muscle cells, induce secretion of connective tissue fibers by these cells, or interfere with the normal processing of lipids by smooth muscle cells or macrophages.

DIABETES MELLITUS

Diabetes mellitus generally is considered to be a major risk factor for coronary heart disease (Pooling Project 1978, Dawber 1980, West 1978, Entmacher et al 1967, Keen et al 1967) Clinical studies have reported that cardiovascular disease is the major reason for death in diabetics. Diabetes unquestionably causes microvascular disease and its complications--renal failure, retinopathy, and small vessel disease of the extremities. It also may promote the development of heart disease by involvement of coronary arterioles and capillaries.

The evidence that diabetes mellitus accelerates atherosclerosis is weaker than for microvascular disease. In the IAP (McGill et al 1968, McGill et al 1981) fatty streaks of the abdominal aorta were no different in diabetics and nondiabetics. Fatty streaks in the coronaries on the other hand were greater in diabetics. As a general rule fibrous plaques in the coronaries also were more extensive in diabetics. The extent of the difference however varied according

to site of involvement and the population under study. Fibrous plaques also were somewhat more prevalent in the abdominal aortas of diabetics. Although the IAP (McGill et al 1968) claimed that diabetics have more atherosclerosis than nondiabetics, the number of diabetics in all categories was relatively small.

The IAP certainly has not been the only autopsy study on the state of arteries in diabetic patients. Several reports claim that atherosclerosis is greater in diabetics (Feldman et al 1954, Thomas et al 1956, Goldenbert et al 1958, Warren et al 1952). An unresolved question however is what group should be used for comparison. Recently, Waller et al. (Waller et al 1980) compared coronary arteries in 229 diabetic patients with 183 control subjects. The diabetics had onset of their disease after age 30. The controls were age and sex matched to nondiabetic patients who died from a fatal coronary event. This study revealed similar severity in narrowing by atherosclerotic plaques in the right, left anterior descending, and left circumflex coronary arteries in nondiabetics with CHD and all diabetics. Some of the diabetic patients had documented CHD; others did not. Thus, on the average, diabetic patients did not have more coronary atherosclerosis than nondiabetics with CHD. This is not to say that diabetics do not have accelerated atherosclerosis. They probably do. Patients with CHD but no diabetes doubtless have more coronary artery disease than those without CHD. The study of Waller et al. (Waller et al 1980) thus implies that diabetics as a group have more atherosclerosis than the whole population of nondiabetics.

The mechanisms of accelerated atherogenesis in diabetic patients remain to be elucidated. Several can be visualized. Microvascular disease of the vasa vasorum may promote filtration of plasma lipids into the arterial wall. Diabetes raises plasma VLDL (Nikkila et al 1973, Abrams et al 1982) and to a lesser extent LDL (Sosenko et al 1980). Increased concentrations of lipoproteins are due mainly to their overproduction. Both high levels and overproduction of these lipoproteins could enhance atherogenesis. Hyperglycemia may cause glycosylation of key proteins of the endothelium or subinternal spaces. Glycosylation thus may increase endothelial damage or enhance deposition of lipoproteins in the arterial wall. Finally, diabetes may promote development of complicated lesions. The disease seems to increase calcification of existing coronary lesions, (Waller et al 1983) and possibly promote coronary thrombosis.

OBESITY

The Framingham Study showed a distinct excess in incidence of cardiovascular disease and death in persons who were overweight (Gordon et at 1976) (Table 10). The relationship held for both sexes, but it was stronger in men. Surprisingly, the Framingham did not find a correlation between body weight and intermittent claudication, but one was found between weight and cerebral infarction. Although obesity in the United States appears to increase the risk for CHD, a strong relation between body weight and extent of atherosclerosis at autopsy has not been observed. The IAP reported that body weight had no definite effect on severity lesions (McGill et al 1968). This study however included several different population groups, and the argument can be made that obesity is a causative factor only in groups at high risk (such as the U.S. public), while not being a cause in low-risk groups. This possibility was examined by Patel et al. (1980) in the Orleans Parish of Louisiana. A positive though weak association between amount of adipose tissue and extent of atherosclerosis was found among whites but not among blacks. In blacks a weak

link was noted between fatty streaks in coronary arteries and adipose thickness. These workers suggested that obesity itself is not an atherogenic agent but is related to one or more atherogenic agents that affect aortas and coronary arteries differently among whites and blacks.

Table 10

Risk Ratios for Body Weight vs.
Cardiovascular Disease Incidence
(Univariant Analysis)
(Framingham Heart Study)

Men		Women	
Body Weight* (% Desirable)	Risk Ratio	Body Weight* (% Desirable)	Risk Ratio
<110	1.0	<110	1.0
110-129	1.4	110-129	1.2
>130	1.9	>130	2.0

* Metropolitan Life Insurance 1959 Desirable Weight Tables.

The connection between obesity and atherosclerosis almost certainly is indirect. There is no reason to believe that excess adipose tissue per se can enhance atherogenesis. On the other hand, obesity has been shown to raise the blood pressure (Duston et al 1980, Sims et al 1982). It also can affect the plasma lipoproteins adversely. Plasma triglycerides and VLDL often are increased in obese patients (Grundy et al 1979). Total cholesterol and LDL levels likewise can be increased, and HDL concentrations are reduced. All of these changes are associated with increased atherogenesis. Studies from our laboratory have demonstrated that obesity is regularly accompanied by increased production of both VLDL and LDL; even when the concentrations of these lipoproteins are not increased, their flux through plasma is. An increased flux of VLDL and LDL may accelerate atherosclerosis independent of their concentrations.

Thus, both epidemiological surveys and clinical studies on the metabolic consequences of overweight suggest that obesity is a secondary risk factor. Autopsy studies on the other hand indicate that it is not a potent atherogenic factor in many people. These postmortum examinations however may be misleading. Obesity probably has little effect when one or more of the primary risk factors-hypertension, hyperlipidemia, and hyperglycemia-- are not induced or aggravated. Many people seem immune to the effects of obesity and in autopsy surveys they could dilute out those who are sensitive and respond adversely in the major risk factors. Unless these two different types of response are kept in mind, the dangers of obesity for many people may be overlooked.

ARTERIAL WALL RESPONSE FACTORS

Much is known about regulation of the primary risk factors. Much less is understood about control on the response of arterial wall constituents to atherogenic influences. Several possible defects in the arterial wall can be

envisioned that could accelerate atherosclerosis. Abnormalities in the vaso vasorum have been considered above. Uncontrolled growth of arterial smooth muscle cells was discussed under the monoclonal theory. This theory may not have been proved, but excessive reaction of smooth muscle cells to injury is a distinct possibility in some patients. Just as keloids represent an exaggerated response to injury to the skin, the cells of the arterial wall under some circumstances might proliferate excessively in response to various forms of injury. The smooth muscle cells could divide at an increased rate, or they could produce unusually large amounts of ground substance and collagen fibers. Almost certainly there is individual variation in the cellular reaction to lipid infiltration into the arterial wall, and differences in degree of response could be highly important for determining who develops enough arterial narrowing to induce clinical ischemic disease. The degree of uptake and accumulation of cholesterol in smooth muscle cells or macrophages also could vary. These differences might be related either to the uptake of lipoproteins or to rates of disposal of excess intracellular cholesterol. These are merely a few possibilities. The molecular biology of the arterial wall should be a fruitful field for future research. It may explain much of the individual variability in atherosclerosis in people who appear to be subject to similar external influences.

DECLINE IN CORONARY HEART DISEASE MORTALITY

Although coronary heart disease still represents the number one cause of death in the U.S.A., rates of CHD are on the decline. Between 1968 and 1976, death rates from CHD declined about 21%, and the reduction was noted for all groups--men and women, black and white. Recent evidence suggests that rates are still in decline. This reduction might be related to either primary "prevention" or secondary "prevention". The former is "prevention" of the onset of CHD, and the latter is prevention of new disease death after the onset of CHD. Presumably, primary prevention would be the product of change in risk factors for CHD, while secondary prevention could result from either modification of risk factors or maintenance of good cardiac function for a longer period. Various authors have attempted to assess the various factors responsible for the decrease in CHD deaths, but to date the decline has not been fully explained. Nonetheless it is interesting to speculate about possible causes.

Perhaps the first question is whether rates of atherogenesis have declined in more recent years. One study that has examined this question is Community Pathology Study in New Orleans. This is a community-wide study of cardiovascular disease as assessed at autopsy in young black and while men (ages 25-44) dying in New Orleans. This study is an outgrowth of the International Atherosclerosis Project (IAP), and it used the same methods for assessing severity of atherosclerosis. The extent of coronary lesions seems to have decreased in white men between 1960-1964 (the IAP) and 1969-1978 (the Community Pathology Study)(Figure 15). In contrast, there was no difference in the average degree of atherosclerosis between 1960-1964 and 1969-1978 in black males (Figure 16). Thus, while reduced atherosclerosis in white males is consistent while a declining rate of CHD mortality in this group, the data are not consistent for black males.

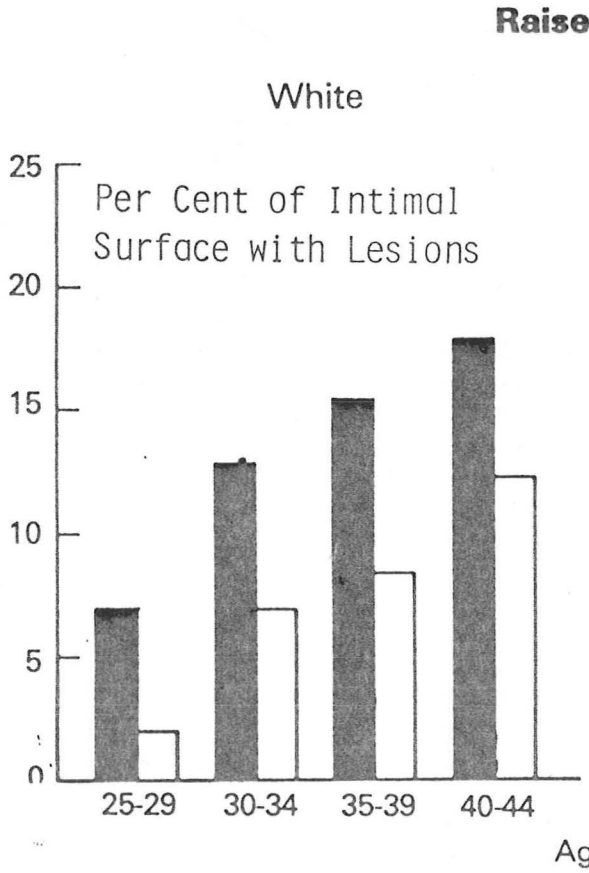


Figure 15

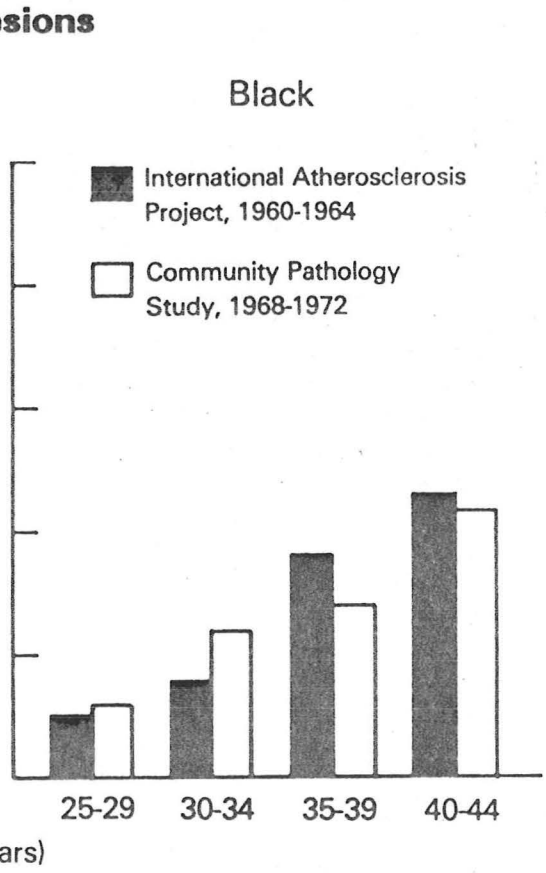


Figure 16

The above findings do not mean that declining deaths from CHD are not due to primary prevention of atherosclerosis. For example, it has been proposed that smoking may increase risk for CHD independent of lesion development, perhaps by promoting the development of coronary thrombosis. There is no question that smoking rates have been declining in white men, and this change may have contributed to reduced smoking on CHD mortality. The best data indicate that smoking among American men declined from 53% to 37% between 1964 and 1975. On the basis of epidemiological studies, it has been estimated that a 2% reduction in smoking rates would produce at least a 1% reduction in coronary mortality. If these relationships are correct, a reduction in smoking of 16% should have produced an 8% decrease in CHD mortality in this men. The reduction in smoking in women has been less, from about 32% to 27%. Thus, Goldman et al (1984) calculated that the overall reduction in CHD mortality attributable to smoking is about 5%. This however may be an underestimate.

Another type of "primary prevention" may be the reduction in cholesterol levels that has occurred over the last two decades. There is strong evidence that cholesterol levels have fallen since 1960, at least 5 mg/dl on the average and possibly as much as 10 mg/dl. Epidemiological studies, such as the Framingham Heart Study suggest that risk for CHD increases 1% for every 1 mg/dl increase in total cholesterol. A crucial question of course has been whether a 1 mg/dl decrease in cholesterol level will produce a 1% decline in CHD rates. The results of the recent Lipid Research Clinics Coronary Primary Prevention

Trials suggests that it does. In this trail there was a high correlation between the decline in cholesterol levels and heart attack rates, and the correlation indeed implied that a 1 mg/dl reduction in plasma cholesterol reduced the rate of heart attack by 1%. If the decline in cholesterol level in the American population has the same impact on CHD rates, then they should have caused a 5-10% decrease in CHD incidence and should have contributed significantly to the overall decline in CHD deaths.

Hypertension is another major risk factor, and it might be expected that the wide-spread use of antihypertensive medications would have had a significant impact on CHD mortality. In fact, however, this has been difficult to show. Epidemiological studies clearly show that the risk for CHD increases with blood pressure, even for blood pressure readings within the "normal" range. Therefore, one might expect that a decline in blood pressure, due to wide usage of antihypertensive medications, would lower CHD rates. the analogy can be made with the cholesterol story. In truth, however, it has not been shown that there is an average decrease in blood pressure levels in the U.S. population, as has occurred for cholesterol. Furthermore, there is not strong evidence from primary prevention trials for blood pressure reduction, as there is from the Lipid Research Clinic trial for cholesterol reduction. It seems clear that treatment of severe hypertension will decrease risk of death, but the number of people falling into the category of severe, well-treated hypertensives, is relatively small compared to the total population; and for this reason, it is difficult to show that treatment of severe hypertensives has contributed measurably to the overall decline in CHD mortality. This of course does not mean that it is not worthwhile to treat severe hypertensives, but it does raise the question of the importance of hypertension therapy for decreasing overall mortality from cardiovascular disease.

The potential for reduction of CHD through lowering of blood pressure throughout the whole population has not been determined. The mean blood pressure for Americans apparently has not declined. However, the idea that a decrease in blood pressure through dietary means (e.g. by reducing the average body weight or decreasing salt intake) is an attractive concept, but to date, there is no evidence that such can be achieved or that it would have a measurable impact on CHD.

Another factor that potentially might contribute to delining mortality from CHD is exercise. The current interest among Americans in staying fit through exercise may have added to the decline in CHD, but there are no data to support this concept. Although several investigators have speculated that increasing exercise will reduce coronary risk, this hypothesis has not been tested.

According to the analysis of Goldman et al (1983) "primary prevention" of CHD has consumed the lion's share of the decline in CHD death. This is not to say that secondary prevention has been unimportant. These workers believe that as much as 40% of the decline can be explained by medical and surgical intervention--coronary care units, clinical treatment of ischemic heart disease, and possibly to a small except by coronary artery bypass surgery. Nonetheless, their analysis provides the striking conclusion that primary prevention can have and indeed has had a major impact on CHD mortality.

SUMMARY

Atherosclerosis is a complex disease that represents the end product of the interaction of many different causative agents. Those which originate external to the arterial wall usually are called the primary risk factors. Many other influences, the secondary risk factors, modulate the primary factors. The penetrance of the secondary factors is variable. They can have a major effect in some people, but not in others. The idea of risk factor is important because it provides the conceptual framework upon which to build in intervention program for prevention of atherosclerosis.

The development of atherosclerosis can be viewed as as two-step process. The first is injury to the arterial wall. The second is response to injury. The primary risk factors can be looked upon as the injurious agents. Examples are factors causing endothelial damage, influx of plasma lipoproteins, toxic products of smoking, hemodynamic injury of hypertension, and perhaps microvascular injury from diabetes mellitus. The response to injury represents typical pathological changes--proliferation of smooth muscle cells, mononuclear infiltration, phagocytosis of products of injury, secretion of connective tissue elements, neovascularization, and necrosis. Regulation of these latter processes is poorly understood and is a worthy subject for future research. Modulation of the primary injurious factors through alteration of secondary risk factors is currently the only significant approach to prevention of atherosclerosis. Future investigation may provide more direct ways to prevent or retard atherogenesis, either by more effective modification of primary factors or by reducing the magnitude of response to these factors.

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