CLUSTERING OF RISK FACTORS

AND

THE METABOLIC SYNDROME

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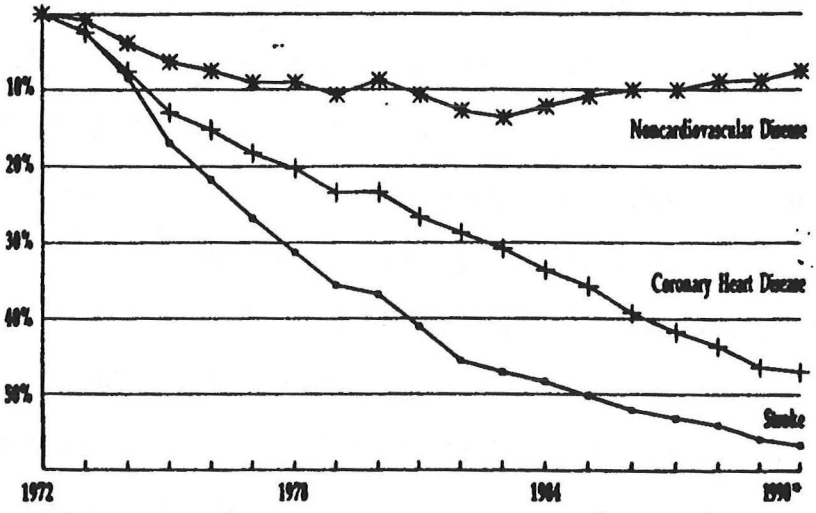
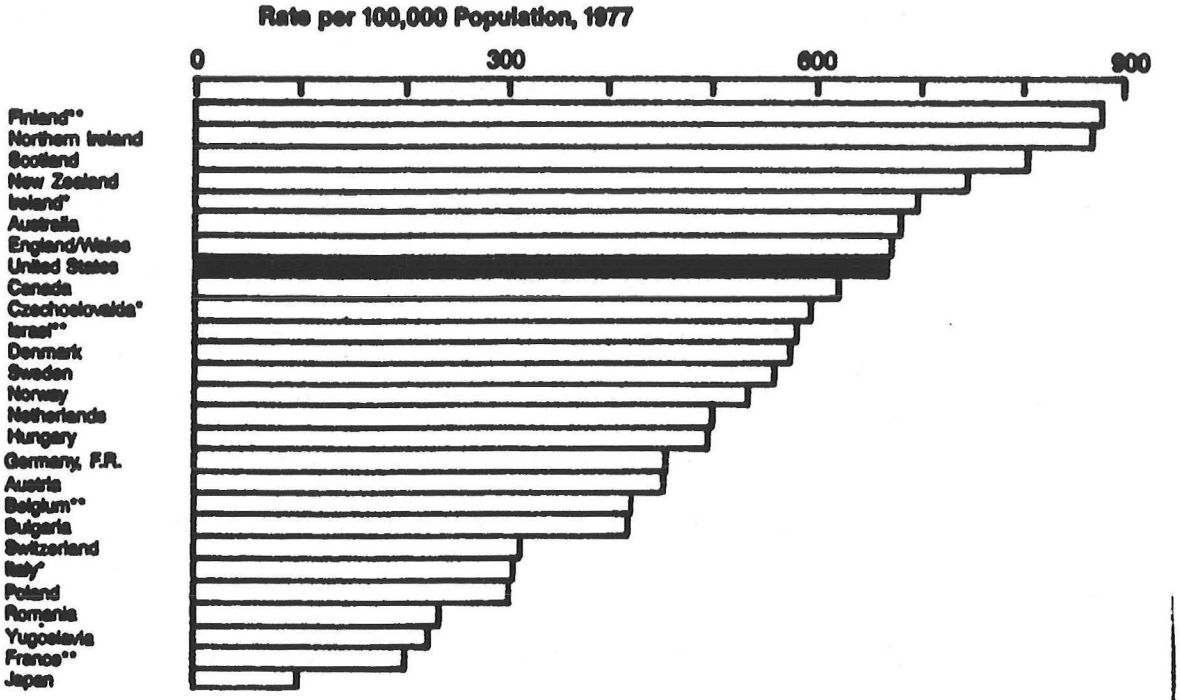
Cardiovascular disease (CVD) continues to be the foremost killer of Americans. Within the broad category of CVD, vascular disease causing coronary heart disease (CHD) and stroke make up the bulk of the problem. In recent years notable advances can be made in the management of patients with established vascular disease. Both morbidity and mortality have been reduced by medical and surgical approaches (1). These approaches are called secondary prevention, and they account for a significant portion of the age-adjusted decline in CVD deaths in the United States that has occurred over the past three decades (Figure 1). Another share of this decline belongs to primary prevention, i.e., to the prevention of new onset CVD. The magnitude of the decrease in CVD mortality obtained through primary prevention efforts has been difficult to define. It may be greater for stroke than for CHD, but for both, some delay in average age of onset is likely. Nonetheless the incidence and prevalence of CVD remain high in the United States; Among many countries the United States remains relatively high in rates of CHD (Figure 2). This fact reflects a failure in primary prevention efforts and a challenge for future preventive efforts.

FIGURE 1. PERCENT DECLINE IN AGE-ADJUSTED MORTALITY RATES SINCE 1972



** Provisional data for 1990.*
Source: NCHS data calculated by NHLBI.

Death Rates for Coronary Heart Disease by Country: Men 35-74 Years of Age Figure 2.



RISK FACTORS FOR CARDIOVASCULAR DISEASE

Primary prevention of CVD must be based on an understanding of causation. Over the past four decades our knowledge of causes of CVD has increased greatly. At the level of epidemiology and clinical practice, these causes are known as "risk factors". The three most important risk factors for the whole population are cigarette smoking, hypertension, and high serum cholesterol (Table 1) (2). Other metabolic abnormalities in addition have been linked to CVD, although their contribution to CVD in the general population is either quantitatively less or is less well understood. These other risk factors consist of various lipoprotein aberrations including high triglycerides and low HDL cholesterol, diabetes mellitus, and modification of hemostasis (3). In the long run the latter group may assume increasing significance, but the impact of three major risk factors nonetheless will remain high. Epidemiologic data (4) indicate that 70 to 80% of the excess risk, for CHD in middle-aged men, i.e. risk above a relatively low baseline level without risk factors, can be attributed to the three major risk

factors. The excess risk beyond this range could be due to other risk factors mentioned, or to factors yet to be identified.

Table 1

MAJOR RISK FACTORS
FOR CORONARY HEART DISEASE

- Cigarette Smoking
- High blood pressure
- High blood cholesterol

An elevated serum cholesterol is the base cause of CHD (Figure 3). Without some elevation of cholesterol concentrations, coronary atherosclerosis rarely develops enough to become clinically manifest. The major component of the serum cholesterol that confers atherogenicity is low density lipoprotein (LDL), but other lipoproteins containing apolipoprotein B (apo B) may be atherogenic as well. The latter include certain triglyceride-rich lipoproteins, notably remnant lipoproteins. LDL and other apo B-containing lipoproteins initiate the atherosclerotic process by filtering into the arterial wall. Atherogenesis is accelerated by a series of changes induced by these lipoproteins and their modified products (e.g. oxidized lipoproteins) (5); these include the chemotaxis of monocytes, activation of macrophages, and formation of foam cells, changes that culminate in the fatty streak, the core lesion of the atherosclerotic plaque.

The atherogenic impact of apo B-containing lipoproteins appear to be blocked to some extent by high density lipoproteins (HDL). High levels of HDL cholesterol reduce risk for CHD whereas low HDL levels predispose to CHD (6). Several mechanisms could explain the protective influence of HDL. For example,

Fig 3

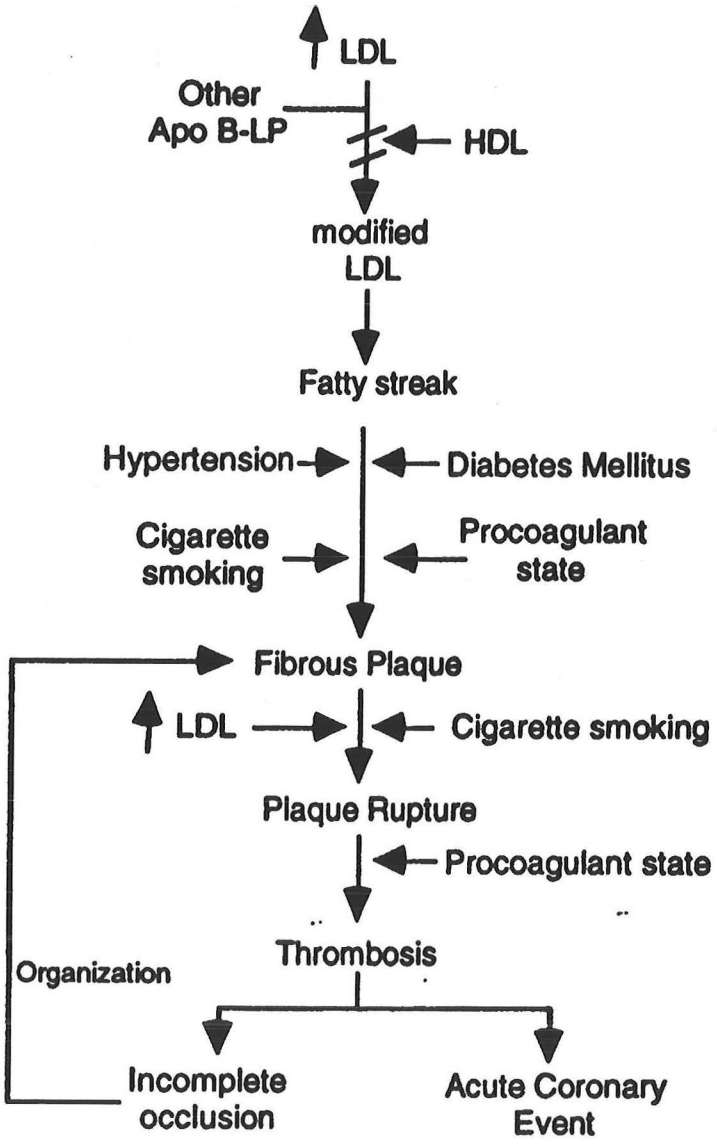


Figure 3. Mechanisms of Atherogenesis
and Acute Coronary Events

HDL may prevent LDL from aggregating (7) and thus may prevent entrapment of LDL within the arterial wall. HDL also may protect LDL against oxidation and thereby reduce its atherogenicity (8). Finally HDL may remove excess cholesterol that has accumulated in foam cells (9).

The second stage of plaque development is conversion of the fatty streak into the fibrous plaque. Hypertension and other risk factors appear to promote this step. Its effect may be mediated through injury to endothelial cells. The fibrous plaque consists of a fibrous cap covering a cholesterol core. To some extent, the fibrous plaque helps to stabilize the lesion. However, lipoprotein infiltration continues at the margins of the plaque to promote lesion extension. At the margin, the fibrous cap is thin, unstable, and prone to the plaque. If rupture occurs, a thrombosis often forms that may precipitate an acute coronary event (i.e. unstable angina pectoris or acute myocardial infarction). Cigarette smoking seemingly increases the likelihood of plaque rupture, possibly by activating macrophages in the lipid-rich region underlying the thin fibrous cap.

The possible role of other risk factors in atherogenesis deserves consideration. The example, the presence of either insulin dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) raises risk for CHD by two-to-three fold (10). Pathological studies suggest that diabetes enhances conversion of fatty streaks into fibrous plaques. Both types of diabetes also predispose to peripheral vascular disease (PVD) and microvascular disease. In middle-aged patients, diabetes is less common than the three major risk factors, and hence its total impact on risk for premature CHD is less. Its incidence progressively increases in older people, and thus its relative importance as a risk factor rises with age. Moreover, most diabetic patients have NIDDM, and the development of hyperglycemia in NIDDM is merely the clinical

manifestation of broader underlying pathology involving glucose metabolism. This pathology comes under the heading of "insulin resistance", and insulin resistance may promote atherogenesis before clinical diabetes actually arises. The mechanisms whereby insulin resistance may predispose to CHD will be discussed subsequently. Insulin resistance may truly be a silent risk factor that is not detected by routine laboratory testing.

Another metabolic factor linked to CHD is an elevation of serum triglycerides. Several potential mechanisms may contribute to this link (Figure 4) (11). For instance, some triglyceride-rich lipoproteins consist of atherogenic remnant lipoproteins. Elevated triglycerides further induce changes in the metabolism of LDL and HDL that could accelerate atherosclerosis. Recent evidence indicates that high triglycerides may also induce a procoagulant state.

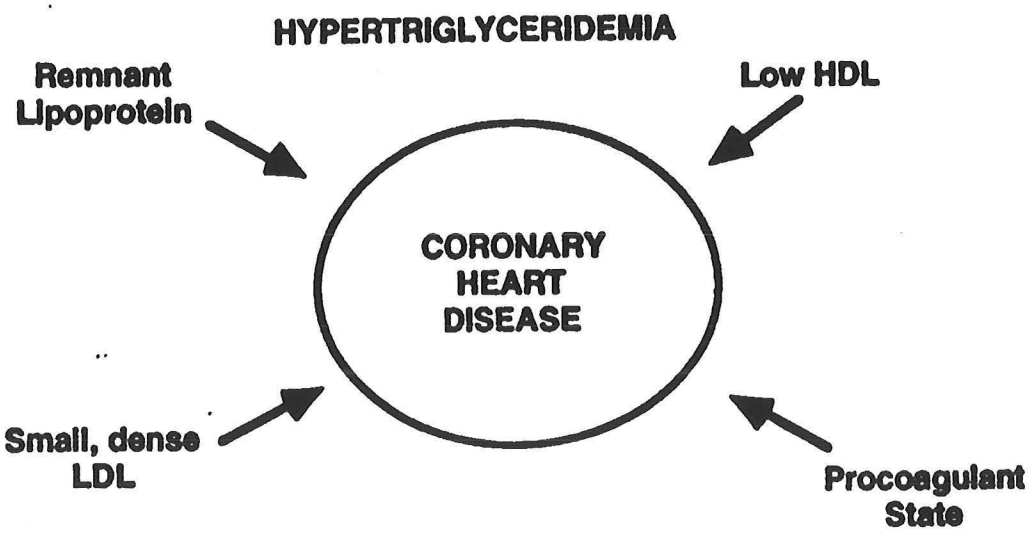


Figure 4. Potential Mechanisms for Atherogenesis and Development of Coronary Heart Disease in Patients with Hypertriglyceridemia

Other lipoprotein aberrations may promote the development of atherosclerosis beyond that which can be attributed to serum levels of

cholesterol and triglycerides. Examples of these aberrations include increases in "small, dense" LDL particles (12), lipoprotein (a) [Lp(a)] (13), and decreases in some specific forms of HDL (e.g. HDL_2 and LpAI) (14,15). The interactions of these specific lipoproteins with the cells of the arterial wall are becoming a subject of great interest. Novel concepts of how these lipoproteins promote atherogenesis are being rapidly developed, and some of these lipoprotein species may assume an independent risk-factor status in the future.

Although an isolated high level of LDL-cholesterol is a common pattern of hyperlipidemia and is a known risk factor for CHD, another pattern frequently observed in patients with CHD consists of a constellation of lipid changes including (a) borderline-high total cholesterol levels (total cholesterol 200-239 mg/dl), (b) mild hypertriglyceridemia (triglyceride 150-250 mg/dl), and (c) relatively low HDL cholesterol levels (35-40 mg/dl in men). All of these changes in fact can be called "borderline" abnormalities that can be distinguished from definite abnormalities, i.e., categorical high plasma cholesterol (total cholesterol >240 mg/dL; LDL cholesterol >160 mg/dL), hypertriglyceridemia (total triglycerides >250 mg/dL), or hypoalphalipoproteinemia (HDL cholesterol <35 mg/dL). Epidemiological data (2) indicate that each of these borderline abnormalities enhances the risk for CHD, and when the risk imparted by each is summed, they equal that of a categorical risk factor, e.g. high-risk LDL cholesterol (>160 mg/dL) or low HDL cholesterol (<35 mg/dL). Because of the common coexistence of these three borderline abnormalities with premature CHD, they can be designated normolipidemic atherogenic dyslipidemia (Table 2). A simple concept of linking atherogenic dyslipidemia to CHD is that each component of the dyslipidemia has a limited atherogenic action, but when combined they have the impact equivalent to a major risk factor. It should be noted that other

lipoprotein abnormalities frequently are present in patients with atherogenic dyslipidemia; these include "small, dense" LDL particles, low HDL_2 levels, and increased remnant lipoproteins. All of these various abnormalities probably contribute to the increased risk accompanying atherogenic dyslipidemia.

Table 2

NORMOLIPIDEMIC ATHEROGENIC DYSLIPIDEMIA

- **Borderline-high serum cholesterol (200 to 239 mg/dL)**
- **Mildly elevated triglycerides (150 to 250 mg/dL)**
- **Low HDL cholesterol (35 to 40 mg/dL)**

Finally there is growing evidence that abnormalities in hemostasis are associated with increased CHD risk. The concept as arisen that a "procoagulant" state predisposes to clinical CHD (16-29) (Table 3). The procoagulant state may enhance conversion of the fatty streak into the fibrous plaque. Moreover, if a person is prone to thrombosis the occurrence of a plaque rupture could produce a large thrombus. If the resulting thrombus is large enough, clinical coronary events will ensue; but if the thrombus is not large enough for clinical symptoms, the plaque nonetheless should enlarge through organization of the thrombus (Figure 3). Several changes in clotting factors have been identified as contributing to a procoagulant state: increased levels of fibrinogen, factor VII, inhibitor of tissue plasminogen activator (PAI-1), and factor X clotting activity. A tendency to platelet aggregation may be another element of the procoagulant state.

Table 3

PROCOAGULANT STATE

Increased Plasma Levels of Coagulation Factors

- **Fibrinogen**
- **Factor VII**
- **Plasminogen activator inhibitor (PAI-1)**
- **Factor X clotting activity**

CLUSTERING OF RISK FACTORS

The Framingham Heart Study and other epidemiological studies indicate that the major risk factors are additive, or perhaps multiplicative (i.e., synergistic) (30). Patients having multiple risk factors are those most likely to develop CHD or other forms of CVD (Figures 5 and 6). An important observation is that several risk factors commonly occur in single individuals. According to the National Health and Nutrition Examination Survey II (NHANES II), 40 percent of people whose blood pressures are $\geq$ 140/90 mm Hg or who are taking antihypertensive medications have serum cholesterol levels $\geq$ 240 mg/dl (31). This is twice the average prevalence of high serum cholesterol (32). A further large percentage of hypertensive individuals will have borderline-high cholesterol levels (200 to 239 mg/dl). Moreover, about 46 percent of people having serum cholesterol levels $\geq$240 mg/dl have blood pressures exceeding 140/90 mm Hg (31). This too is a doubling of the prevalence of hypertension. Furthermore, patients with NIDDM have an increased prevalence of both hypertension and lipid disorders. For example, the prevalence of hypertension in diabetic patients is almost twice that of nondiabetic controls (33). The prevalence of various forms of hyperlipidemia and dyslipidemia varies among

different population groups of NIDDM patients. Regardless of the particular population group, however, NIDDM patients usually have two-to-three fold higher rates of abnormal lipid levels than do nondiabetic controls (34-37). The World Health Organization multinational study of vascular disease in diabetic subjects (38,39) reported high frequencies of both hypercholesterolemia and hypertriglyceridemia in NIDDM patients. Additionally, in NIDDM patients from the Framingham Heart Study (35) and from a study of Hispanic and nonhispanic whites (40), the excess of dyslipidemia appeared mainly as hypertriglyceridemia, increased VLDL cholesterol, and low HDL cholesterol levels. In both groups however the majority of NIDDM patients had total cholesterol >200 mg/dL, i.e. borderline high cholesterol levels. The latter study (40) indicated that lipoprotein abnormalities may precede onset of definite hyperglycemia by several years. All of these studies reveal a strong tendency for clustering of risk factors in the general population, and individuals manifesting multiple risk factors are those most likely to develop premature CVD.

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Figure 5

Risk of Cardiovascular Disease at Systolic Pressure of 150 mm Hg According to Intensity of Other Risk Factors

Subjects Aged 45 Years, Framingham Study 18-Year Follow-Up

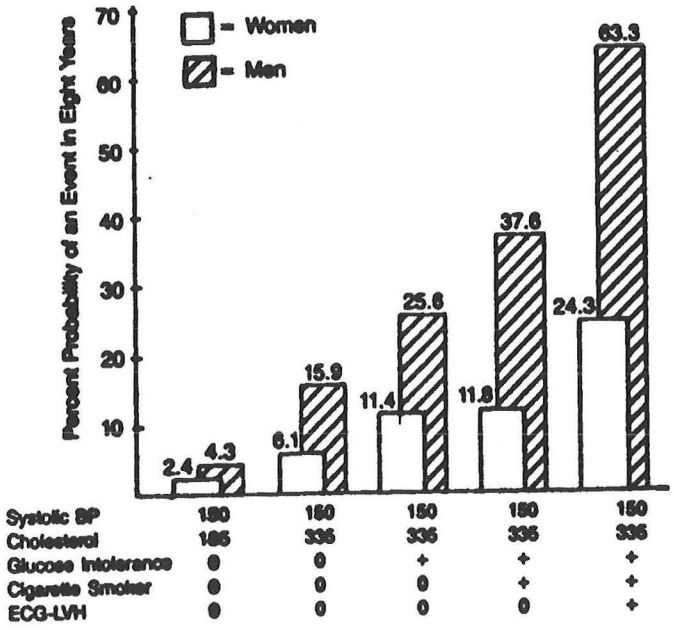
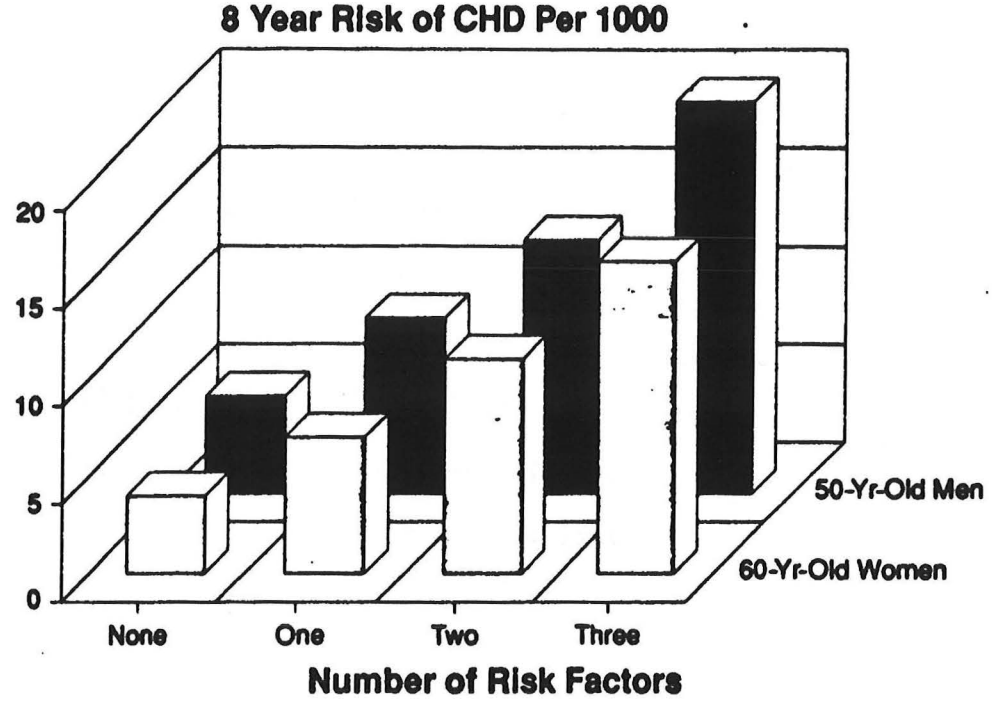


Figure 6
Predicted CHD Incidence By Number of Risk Factors



Risk factor defined as: Cholesterol ≥ 240 mg/dL; Systolic Blood Pressure ≥ 140 mm Hg; Cigarette Smoking

Source: Harlan WR, Garrison RF. Framingham Data. National Heart, Lung, and Blood Institute, Bethesda, MD. 1990.

THE METABOLIC SYNDROME

The clustering of multiple risk factors appears to occur commonly enough to justify calling this aggregation a syndrome. Since the associated risk factors--dyslipidemia, insulin resistance with or without diabetes mellitus, and hypertension--are of metabolic origin, their clustering in a single patient has been designated the "metabolic syndrome". These three risk factors together can be named the "metabolic triad". Of importance, the metabolic syndrome can manifest in several ways. In one form, the coexisting risk factors occur as categorical abnormalities, i.e., clinical hyperlipidemia, hypertension, and hyperglycemia (Table 4). When these three risk factors coexist, patients carry high risk for premature CVD. Increasingly recognized is another abnormality commonly present in the metabolic syndrome, namely, hemostatic changes, i.e., producing a procoagulant state.

Table 4

THE METABOLIC SYNDROME

Clinical Syndrome

- Noninsulin dependent diabetes mellitus (NIDDM)
- Hyperlipdiemia (or hypoalphalipoproteinemia)
- Clinical hypertension

Another form of the syndrome is one in which metabolic aberrations are borderline and do not reach the severity of categorical abnormalities (Table 5). The lipoprotein pattern of the former consists of normolipidemic dyslipidemia without hyperlipidemia (i.e., without elevated cholesterol or triglycerides). Glucose metabolism reflects the stress of insulin resistance, but fasting normoglycemia is maintained. And blood pressure is in the high-normal zone, but not categorically elevated. Epidemiological data (30) indicate that the sum of these borderline changes significantly increases the risk for CVD and warrants calling the borderline form of the metabolic syndrome a "risk factor" for CVD.

Table 5

THE METABOLIC SYNDROME

Subclinical Syndrome

- Insulin resistance
- Normolipidemic, atherogenic dyslipidemia
- High-normal blood pressure

SEARCH FOR A SINGLE CAUSE OF THE METABOLIC SYNDROME

Since risk factors so often cluster in single individuals the question naturally arises whether there might be a common cause the metabolic syndrome. In particular, can a single metabolic defect produce glucose intolerance, dyslipidemia, and blood-pressure elevation? In recent years, investigators in the diabetes field have postulated that single abnormalities in glucose and insulin metabolism underlie the metabolic syndrome. According to a favored hypothesis, multiple risk factors are the consequence of a metabolic abnormality called "insulin resistance". Without question, abnormalities in levels of plasma glucose, plasma lipids, blood pressure and cardiovascular disease frequently occur simultaneously with high insulin levels (41-51). Since elevated insulin concentrations normally produce hypoglycemia, when euglycemia or hyperglycemia coexist with hyperinsulinemia, a state of insulin resistance must be present.

Many workers note that hyperinsulinemia is not invariably accompanied by all components of the metabolic triad (114). This undoubtedly is true; but borderline changes in plasma glucose and lipids and blood pressure nonetheless may be present even when categorical abnormalities are absent. As mentioned before, these borderline abberations when occurring together can subsequently increase the risk for CHD (30). Thus the total impact of insulin resistance on CHD risk factors may not be fully appreciated. Furthermore, if insulin resistance causes only one or two elements of the metabolic triad in a given person, the risk for CHD may still be appreciably increased. The mechanisms whereby hyperinsulinemia (or insulin resistance) might induce the metabolic syndrome are at present largely speculative. They will be considered in more detail later in the article. But regardless of mechanism, the association is

common; the issue thus is not association, but rather, whether the relationship is one of cause and effect.

Clearly, if a single metabolic factor is responsible for the changes in glucose levels, lipid levels, and blood pressure, it must be a factor that influences the metabolism of all of these systems. Such a factor might not produce raised insulin levels; however such generalized metabolic abnormalities without elevated insulin concentrations so far have not been detected. Possibly when defects having manifold metabolic consequences occur they all result in high insulin levels. If so, hyperinsulinemia may be a marker for defects that induce generalized metabolic changes. Thus, there could be several different causes of insulin resistance and hyperinsulinemia, and each could set into motion changes that lead to the metabolic syndrome. Consideration therefore might be given to the causes of insulin resistance.

METABOLIC MECHANISMS FOR INSULIN RESISTANCE

Human metabolism is affected by a variety of factors and several of these theoretically could induce insulin resistance. Included in this list are genetic factors, aging, obesity, the composition of the diet, the type and level of physical activity, and drugs. Insulin resistance could result from a generalized metabolic defect that is expressed in all tissues; or it could be selectively expressed in certain tissues. The major site of insulin-mediated glucose disposal is skeletal muscle (52), and muscle has received prime consideration for the predominant site of insulin resistance. However, other possible sites of origin include adipose tissue, liver, the vasculature, and endocrine organs. These different sites can be reviewed as potential candidates for the origins of insulin resistance.

Skeletal Muscle

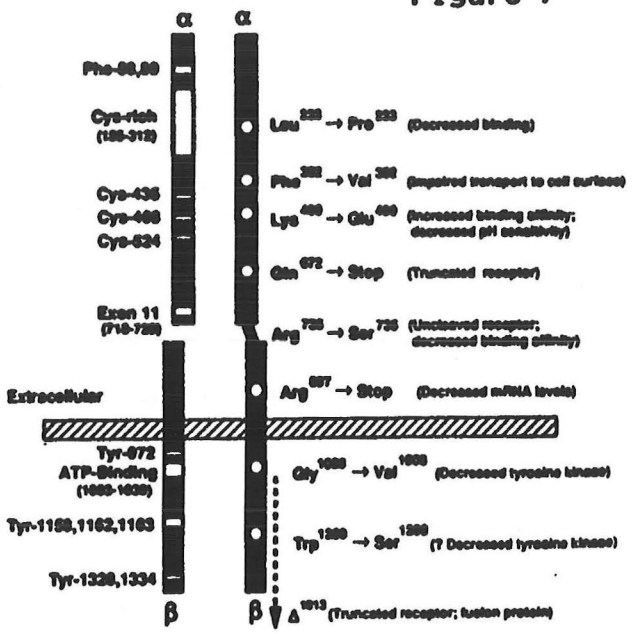
One cause of insulin resistance could be a defect in normal action of insulin or glucose metabolism in skeletal muscle. Several candidate genes in pathways of insulin and glucose metabolism have been proposed (Table 6). Most genetic defects identified to date affect insulin receptor protein (53). At least 35 different defects in insulin receptors have been identified, and these manifest in three different syndromes: the Type A syndrome, the Rabson-Mendenhall syndrome, and Leprechaunism (Figure 7). The Type A syndrome, the most common, usually presents in adolescent girls having hirsutism or menstrual irregularities, besides hyperinsulinemia and glucose intolerance. Most of the Type A patients under investigation are adolescents or young adults, and occurrence of the full metabolic syndrome has not been reported. Insulin resistance also has recently been found with a common variant of the insulin receptor substrate-1 (54). This defect also induces significant insulin resistance when accompanied by obesity; and in such cases, affected persons manifest a clustering of metabolic risk factors including raised fasting plasma glucose, hypertriglyceridemia, and high levels of plasma tissue-plasminogen-activator PAI-1

Table 6

CANDIDATE GENES FOR INSULIN RESISTANCE

- Insulin receptor
- Insulin receptor substrate -1
- RAD gene ("Ras associated with diabetes")
- Insulin stimulated protein kinase-1
- Protein phosphatase 1
- Glycogen synthase
- Glucose transporters (GLUT 4)
- Hexokinase II

Figure 7



Taylor et al.
Diabetes Care 13:257, 1990

Investigation of other candidate genes for primary insulin resistance in muscle tissue have been less revealing. A search for abnormalities in the genes encoding for glucose transporters (GLUT-4), glycogen synthase, and hexokinase II continues, but so far such defects have not been identified (52). Most patients with insulin resistance appear to have a "post-receptor" defect in glucose metabolism (55,56), and in spite of the central role of the above gene products in the metabolism of glucose in muscle, a common polymorphism in one or more of these genes contributing to insulin resistance remains to be found.

Perhaps the most common cause of insulin resistance in skeletal muscle is secondary to high plasma levels of free fatty acids (FFA) which suppress glucose oxidations. The mechanisms for increased FFA levels will be considered later. This competition between glucose and fatty acids for oxidative fuel is known as the glucose-fatty acid cycle of Randle (57) (Figure 8). When fatty acids become the preferred substrate for oxidation because of their abundance, a post-receptor "defect" in glucose utilization occurs, and insulin resistance develops (58).

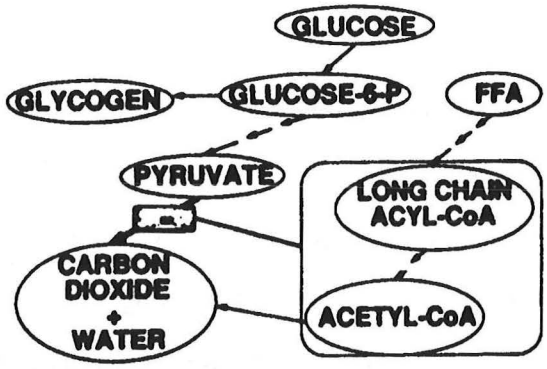


FIGURE 8

Operation of Randle's cycle in the skeletal muscle. Increased FFA supply/oxidation causes a buildup of long-chain acyl-CoA and acetyl-CoA, which in turn inhibit PDH and glucose oxidation.

Another important cause of insulin resistance in skeletal muscle is lack of exercise (59,60). Several mechanisms may contribute. Disuse leads to muscle atrophy and a reduction in available muscle mass to oxidize glucose. In addition, exercise appears to stimulate carbohydrate utilization which enhances insulin sensitivity; therefore, lack of exercise reduces insulin sensitivity. In the United States public at large, sedentary life habits probably enhance insulin resistance in a large portion of the population.

Finally, insulin sensitivity in muscle declines with age (61). This change could be largely secondary to increasing body fat, decreasing exercise, and loss of muscle mass with aging. However, it also is possible that metabolic efficiency declines as people age, and this too could play a role. However, it is likely that increasing the ratio of lean body mass to adipose tissue through regular exercise and weight control could improve insulin sensitivity in older people.

Adipose Tissue

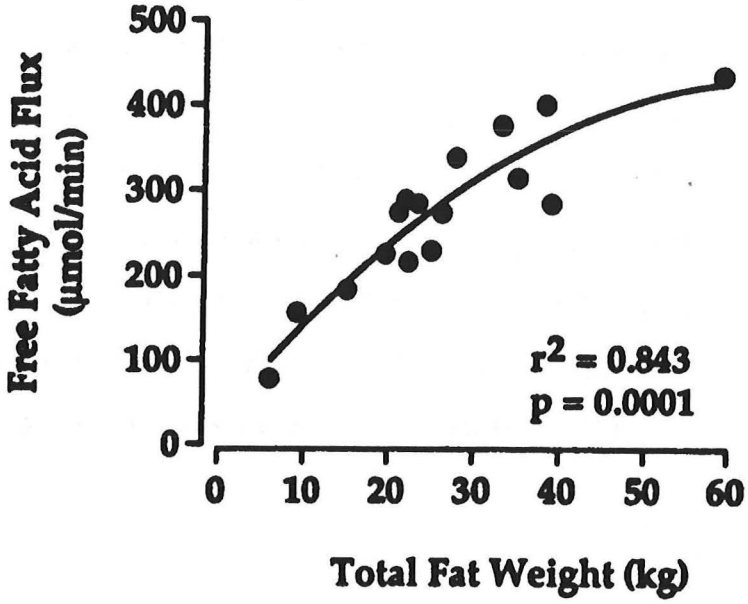
High levels of insulin normally suppress lipolysis of triglycerides decreasing release of free fatty acids (FFA) by adipose tissue. Thus, amounts

of FFA entering plasma are insulin dependent. When adipose tissue is insulin resistant, high insulin levels fail to suppress FFA release, and plasma FFA levels are abnormally high despite hyperinsulinemia (52). A high FFA level in turn induces insulin resistance in muscle through the fatty acid-glucose cycle (58). Several changes in adipose tissue metabolism may lead to insulin resistance states.

A rare example of insulin resistance involved with adipose tissue is the complete absence of adipose tissue--a condition called generalized lipodystrophy (62). The failure to store fatty acids in adipose tissue results in their division to liver and muscle. The result is marked insulin resistance in muscle, fatty liver and marked hypertriglyceridemia, and eventually diabetes mellitus (63). In a related condition, partial lipodystrophy, hyperlipidemia and diabetes also are typical.

The most common "abnormality" in adipose tissue producing insulin resistance is obesity. Excess accumulation of fat in adipose tissue results in a high secretion of FFA into the circulation (Figure 9) (64-66). For some reason, in most obese individuals, even high levels of insulin cannot suppress FFA levels to the normal range. As obesity and insulin levels increase, increments in FFA release are dampened (Figure 9); but FFA levels nonetheless remain high (67). The high FFA levels, resulting from insulin resistance, appear to induce the metabolic triad, and perhaps a procoagulant state, in many people.

Figure 9



Generalized obesity usually produces an insulin resistance state. Even so different adipose tissue deposits in their propensity to insulin resistance seems to vary. For example, adipose tissue located in the abdomen apparently is more prone to insulin resistance than is that in gluteofemoral regions (68-70). The pattern of fat distribution thus affects the overall insulin sensitivity of the body. The influence of different distribution patterns is particularly evident in the obese state. In men, excess fat usually accumulates in the abdominal or truncal region, whereas in women, a gluteofemoral distribution is more common. Abdominal accumulation is reported to be particularly adverse (68-70). Causes of differences in fat distribution are not fully understood. In spite of usual gender differences, there can be different patterns of fat distribution within the sexes. Fat distribution appears to be determined in part by genetic factors, and any genes that promote abdominal obesity should enhance insulin resistance.

Recent investigations from our laboratory (71,72) indicate that the total fat on the trunk has a greater impact on insulin sensitivity than does fat localized within the abdomen (Figure 10). Truncal fat includes intraabdominal

fat, subcutaneous fat around the abdomen, and subcutaneous fat over the chest. Although intraperitoneal fat has been reported to be particularly adverse for producing insulin resistance (70), the total amount of fat in the trunk substantially exceeds that within the abdomen (71,72). This total truncal fat thus seems to outweigh the impact of the lesser amount of fat localized in the abdomen. Moreover excess truncal fat was found to have a greater suppressive effect on insulin-mediated glucose uptake than does extra fat in peripheral locations.

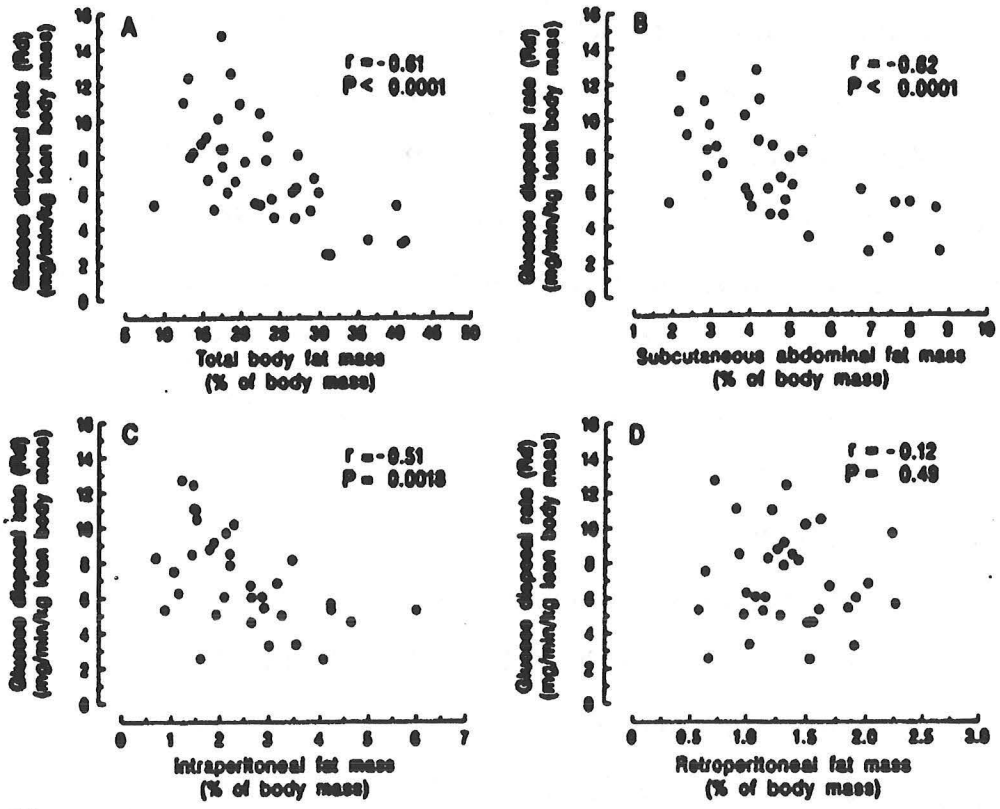


Figure 10. The relationship of insulin-mediated glucose disposal rate (R_d value, during euglycemic, hyperinsulinemic glucose clamp study at 40 $mU/m^2 \cdot min$ insulin infusion rate) and total body (A), subcutaneous abdominal (B), intraperitoneal (C), and retroperitoneal (D) fat masses. Abate, Garg et al. JCI 96:88-98, 1995.

The discovery of a gene linked to obesity in mice raises the question whether a defect in a single gene affecting energy balance might produce insulin resistance and the metabolic syndrome through its influence on total body fat content (73). This gene encodes for a circulating protein that suppresses the appetite and produces satiety. In the genetic absence of this protein, appetite is increased and obesity is induced. There is strong evidence that human obesity has a genetic component; consequently, a single genetic defect in appetite regulation could engender the obese state; this in turn could induce the metabolic syndrome.

Primary insulin resistance could originate in adipose tissue as well as in skeletal muscle (74,75). Candidate genes for insulin resistance in adipose tissue could include all those listed for skeletal muscle. The list of potential influences for adipose tissue can be expanded to include lipoprotein lipase, fatty acid transfer proteins, hormone-sensitive lipase, lipolytic beta-adrenergic receptors, glucocorticoid receptors, and androgen receptors (Table 7) (74,75). According to some investigators, defects in fatty acid metabolism in adipose tissue may as likely induce insulin resistance as abnormalities in glucose metabolism in muscle. Specific abnormalities in the various candidate defects in adipose tissue however have not been identified.

Table 7

CANDIDATE GENES
FOR INSULIN RESISTANCE

Adipose Tissue

- Same as for skeletal muscle (see Table 6)
- Hormone sensitive lipase
- Hormone receptors
- Lipoprotein lipase
- Fatty acid transport proteins

Liver

A third insulin-sensitive tissue is liver. Insulin resistance in liver is reflected by a failure of insulin to suppress hepatic glucose output (52). This output is largely due to gluconeogenesis, and normally, high insulin levels suppress hepatic gluconeogenesis and glucose output. A persistent high output of glucose that is not suppressed by normal insulin levels could induce hyperinsulinemia and lead to insulin resistance in muscle. Further, the failure of insulin to act normally in the liver might result in increased synthesis and secretion of VLDL triglycerides, another component of the metabolic syndrome.

Endocrine Origins of Insulin Resistance

Another candidate mechanism for insulin resistance is primary overproduction of insulin by pancreatic beta-cells. Excessive secretion of insulin on a genetic basis should down regulate insulin receptors on muscle cells and hence produce insulin resistance. High levels of insulin on this basis further could drive the lipid and blood pressure abnormalities of the metabolic syndrome. The finding of high insulin levels in nonobese relatives of NIDDM patients is consistent with the existence of this mechanism. However, a specific metabolic defect leading to a primary overproduction of insulin has not been identified.

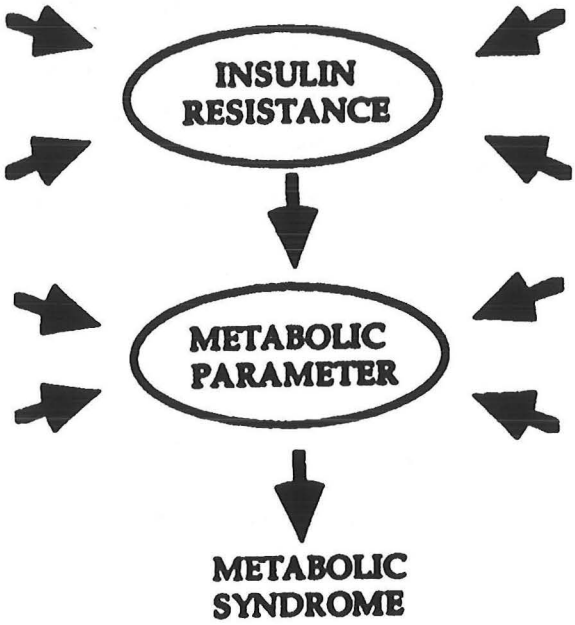
Androgens may induce insulin resistance by enhancing truncal obesity. This action of androgen is common in men, but also occurs in women. About 20% of premenopausal women have the male pattern of fat distribution. This distribution in women could be the result of excessive androgen production by the adrenal gland. Further, women having polycystic ovaries typically have truncal fat

deposition and insulin resistance (76). These responses appear to be related to excessive ovarian production of androgens. Finally, glucocorticoids alter carbohydrate metabolism and induce insulin resistance. Some investigators speculate that excessive activity or responsiveness to glucocorticoids may contribute to the insulin resistance and the metabolic syndrome in some people (74).

MULTIFACTORIAL CAUSATION OF RISK FACTORS

The hypothesis that single genetic defects can produce the metabolic syndrome is feasible and serves as a stimulus to the investigation of the molecular basis of risk factors. If there are common genetic polymorphisms in the general population that cause the metabolic triad, however, they may induce only moderate forms of the syndrome; even so, only moderate changes in risk parameters can raise the likelihood for developing CHD. When the syndrome exists in more severe forms, multiple influences probably act together to worsen risk factors. Single defects with multiple metabolic consequences thus may be the foundation of the syndrome and predispose to it; but they probably cannot entirely account for the clustering of categorical risk factors. This is an important consideration for primary prevention of CVD because other contributing influences on risk factors may be alternate targets for preventive measures. In the discussion to follow, the hypothesis will be examined that a metabolic derangement, which is manifest by insulin resistance, predisposes to the metabolic syndrome; at the same time, other influences that can worsen the risk factors are required for the full-blown syndrome (Figure 11). This hypothesis will be examined with respect to each of the risk factors of the metabolic triad.

Figure 11



Noninsulin Dependent Diabetes Mellitus (NIDDM)

Investigations of the past decade provide a better understanding of the pathogenesis of NIDDM. For clinical hyperglycemia to develop, two general abnormalities must come into play. One is insulin resistance; the other is a decline in insulin secretion. Many people have prolonged insulin resistance and yet never develop NIDDM; they are able to mount sufficient hyperinsulinemia to maintain a normal level of plasma glucose. In some people however high concentrations of plasma insulin cannot be sustained, and plasma glucose levels begin to rise. When the hyperinsulinemic response is blunted enough hyperglycemia develops; this rise in glucose levels defines clinical NIDDM (Figure 12). An insufficient response in insulin secretion thus can be considered a second abnormality required for development of NIDDM.

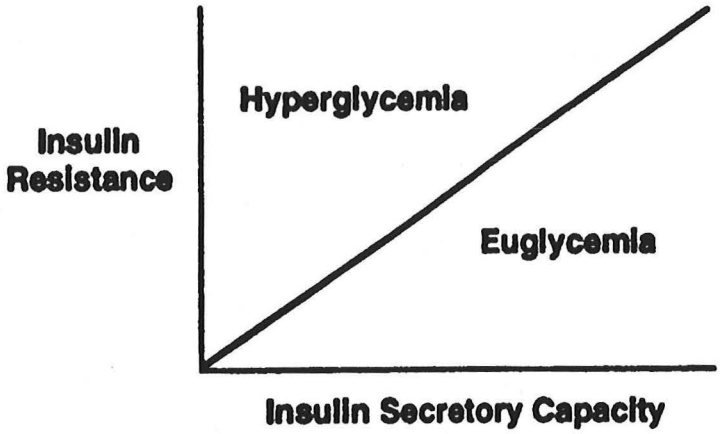


Figure 12. Theoretical Relationship Between Insulin Secretory Capacity and Insulin Resistance in Development of Hyperglycemia

A decline in secretion of insulin theoretically could result from a decrease in the mass of pancreatic beta-cells or from a decline in their function. Many NIDDM patients have been found at postmortem to have a significant loss of beta-cell mass (77-79). The etiology may be variable. One contributor could be an inevitable loss of beta-cells with aging. Another possibility is that prolonged overproduction of insulin secondary to insulin resistance results in beta-cell "exhaustion". Moreover, insulin overproduction is accompanied by a high secretion rate for amylin, and precipitation of this peptide in turn could destroy beta-cells (80). Recently another hypothesis has been suggested, namely, that prolonged elevation of plasma FFA accompanying insulin resistance may engorge beta-cells with excess triglyceride and kill them (81). Both mechanisms of cell death, i.e. amyloid deposits and lipotoxicity, could be the result of prolonged insulin secretion. That prolonged insulin resistance eventually reduces beta-cell mass is an attractive hypothesis but it does not exist the list of possible causes.

Another type of beta-cell abnormality could be a genetic defect that impairs insulin secretion. If such defects exist, they could lead to development of hyperglycemia in the face of insulin resistance. Several candidate defects have been suggested; two of these are a defect in glucose transporters (e.g. GLUT-4) (82) and mutations in glucose kinase (83,84). The latter have been found in some cases of maturity onset diabetes in the young (MODY). Defects in glucokinase however have not been identified in patients with typical NIDDM. A functional defect in insulin secretion also might be acquired. For example, high glucose levels accompanying insulin resistance may impair the beta-cell's ability to secrete insulin. Support for this mechanism comes from the observation that insulin secretion can improve during caloric restriction in obese patients with NIDDM.

Atherogenic Dyslipidemia and Hyperlipidemia

Borderline-high and high total cholesterol. Some elevation of serum total cholesterol is required for the initiation of atherosclerosis, and with greater elevations, atherogenesis is accelerated. A borderline-high serum cholesterol thus is an essential component of atherogenic dyslipidemia. This is often overlooked when defining the atherogenic phenotype. Causes of borderline-high cholesterol levels include excessive intakes of saturated fatty acids and cholesterol, obesity, aging, and genetic factors (85). The latter become particularly important in the etiology of moderate hypercholesterolemia (total cholesterol 240 to 280 mg/dL).

Insulin resistance could raise serum cholesterol levels in at least two groups. First, it could enhance the secretion of apo B-containing lipoproteins from the liver. For example, lipoprotein kinetic studies indicate that obesity,

which induces insulin resistance, enhances the number of apo B-containing lipoproteins secreted by the liver (86,87). This increase may not be the result of higher FFA levels per se. Other conditions, e.g. high carbohydrate diets and alcohol ingestion, enhance hepatic triglyceride synthesis and raise VLDL-triglyceride levels; but these factors merely increase the triglyceride content of VLDL particles and do not raise the number of particles secreted into plasma. Thus, the hyperinsulinemia (or insulin resistance) accompanying obesity may be responsible for an increase in the number of lipoprotein particles secreted; this response could raise cholesterol levels.

Insulin resistance further may reduce the activity of LDL receptors. This possibility arises because of the finding that clearance rates for LDL decline with age. Since insulin resistance rises with age, it could contribute to a reduction in LDL clearance (i.e. LDL-receptor activity). Insulin has been shown to increase LDL-receptor activity in tissue culture, and this activating influence could be lost in a state of hepatic insulin resistance. A significant portion of this effect could be secondary to increasing obesity with age, but a generalized decline in metabolic efficiency with aging, which could lead to insulin resistance, could be another cause.

Even if insulin resistance plays a role in the rise of cholesterol levels with age, it is not the sole factor affecting cholesterol levels in middle age. This is illustrated by cholesterol levels in Pima Indians. This population of native Americans appears to have a genetic form of insulin resistance that is accentuated by a high prevalence of obesity. Even so, they have relatively low serum cholesterol concentrations. Lipoprotein kinetic studies suggest that they have an inherently high activity of LDL receptors, presumably on a genetic basis (88). The insulin resistance of Pima Indians may raise their cholesterol levels

to some extent, but favorable genetic factors protect them from hypercholesterolemia.

By the same token, genetics undoubtedly modulate cholesterol levels in other populations. Although most Americans show a rise of LDL-cholesterol levels with aging, final concentrations in middle age vary widely. Since dietary intake is relatively constant in the general public, genetic factors must account for a significant portion of the variation in cholesterol levels. Estimates suggest that genetics explains about 50 percent of the variation. A variety of genes potentially affect LDL-cholesterol levels, and polymorphisms in several of these genes could explain this variation. Thus, the interaction of insulin resistance and genetic factors may largely determine cholesterol levels of middle-aged and older adults.

Another element of atherogenic dyslipidemia is the presence of "small, dense" LDL particles. These particles often are secondary to moderate increases in plasma triglycerides (89), which have an insulin-resistance contribution, but seemingly there is an independent genetic influence determining their presence (90). Several studies have suggested that "small, dense" LDL particles are a component of the "insulin-resistance" syndrome, but whether the insulin-resistance component is independent of elevated triglyceride levels is uncertain at present.

Hypertriglyceridemia. The concept that primary insulin resistance contributes to elevated plasma triglycerides is intriguing. Reaven et al (91) have long postulated that high insulin levels stimulate the production of VLDL triglyceride and thus raise plasma triglycerides. This mechanism has been questioned by some because exogenous insulin administration to diabetic patients

reduces triglyceride levels; but even so, insulin resistance may predispose to hypertriglyceridemia. For example, hypertriglyceridemic patients have concomitant defects in glucose metabolism that are characteristic of insulin resistance (92). Further, hypertriglyceridemic patients frequently have hyperinsulinemia, which is characteristic of insulin resistance. Insulin resistance secondary to obesity moreover is commonly accompanied by high triglyceride levels. One mechanism likely is the increased level of FFA accompanying obesity; a high FFA promotes hepatic FFA uptake and stimulates VLDL triglyceride production. Whether obesity induces other metabolic changes (e.g. increased lactate production), which enhance VLDL- triglyceride secretion, is uncertain. It must be noted that high FFA levels inherently reflect insulin resistance in adipose tissue, and in this sense, hypertriglyceridemia must be a consequence of insulin resistance, whether primary or secondary in origin.

Although overproduction of VLDL triglycerides due to insulin resistance tends to raise plasma triglycerides, many people seemingly can rapidly hydrolyze excess plasma triglycerides and thus prevent hypertriglyceridemia (93). For example, many obese people overproduce VLDL triglyceride but maintain normal plasma triglyceride levels because of rapid catabolism of triglyceride-rich lipoproteins. This suggests that only those individuals having a concomitant lipolytic defect develop hypertriglyceridemia; if true, genetic or metabolic defects in plasma triglyceride lipolysis play a critical role in concert with insulin resistance in causation of hypertriglyceridemia.

<u>High Density Lipoproteins (HDL)</u>. Several lines of evidence suggest that insulin resistance predisposes to low HDL-cholesterol levels. For example, Garg et al. (94) noted in young adult men that HDL-cholesterol levels are inversely related to glucose disposal as measured by the glucose-clamp study. Further,

Karhappa et al (95) reported that "isolated" low HDL levels in the absence of obesity are characterized by insulin resistance. And Abate et al. (96) recently published that NIDDM patients with normal plasma lipids typically have low plasma HDL cholesterol, and these low levels are independent of obesity; since most NIDDM patients are insulin resistant, the reduced HDL-cholesterol concentrations could be due to insulin resistance.

In addition, the obese state, an insulin-resistant condition, is typified by low HDL-cholesterol levels. All of the metabolic consequences of obesity are not understood, but insulin resistance induced by obesity may be one cause of low HDL levels. Abdominal or truncal obesity seems to be particularly associated with reduced HDL-cholesterol levels. Furthermore, cigarette smoking is known to lower HDL concentrations, and part of this effect could be related to the tendency of prolonged smoking to induce abdominal obesity.

Certainly other factors besides insulin resistance affect HDL levels, and may contribute to reduced levels. Some of these factors include increased triglyceride levels, reduced activity of lipoprotein lipase, increased activity of hepatic triglyceride lipase, increased activity of cholesterol ester transfer protein, and decreased production of apo AI. Although the degree of insulin sensitivity might influence these factors as well, they undoubtedly are affected by other influences as well. For example, Cohen et al (97) recently reported that genetic variation in the gene encoding for hepatic triglyceride lipase significantly affects the variation in HDL-cholesterol levels in the general population. The same is true for variation at the gene locus that encodes for apo AI, apo CIII, and apo AIV. Thus, the low HDL-cholesterol levels that are found in many patients with atherogenic dyslipidemia cannot be explained entirely by insulin resistance.

Hypertension

The third component of the metabolic triad is hypertension. Elevated blood pressure is commonly observed in patients with NIDDM, and it frequently presents in those with hyperlipidemia. These common associations raise the possibility that a single metabolic defect underlying glucose and lipid metabolism extends to blood pressure. It is well accepted that obesity is a frequent cause of high blood pressure, perhaps the most common cause in middle-aged adults. Since obesity is accompanied by insulin resistance and hyperinsulinemia, the question has been raised whether insulin resistance can account for the hypertensive effect of obesity. This question has been the subject of much speculation, and support for the hypothesis comes from research in animal models. One element of the hypothesis is the concept of selective insulin resistance, i.e., some tissues (e.g. skeletal muscle) are insulin resistant, whereas other tissues (e.g. kidney and central nervous system) remain insulin sensitive. At least three mechanisms have been postulated whereby hyperinsulinemia may increase the blood pressure. These include sodium retention, increased sympathetic nervous system activity, and hypertrophy of vascular smooth muscle cells. Although some workers favor hyperinsulinemia and selective insulin resistance as the cause of hypertension, others (98) postulate that hypertension is secondary to total insulin resistance. According to the latter hypothesis, a lack of insulin action in vascular smooth muscle cells disrupts normal transmembrane flux of ions; the most important of these may be an increase in intracellular calcium which will cause arteriolar vasoconstriction. It is thus possible that both types of insulin resistance come into play to raise the blood pressure.

Many middle-aged hypertensive patients are not obese, and hence are not subject to the blood pressure raising actions of obesity. Thus we must ask

whether hypertension in some nonobese people can be explained by primary insulin resistance. At least two reports (99,100) indicate that hypertensive patients frequently have elevated insulin levels even when they have normal body weight and normal glucose levels. These patients presumably have a primary form of insulin resistance. Some investigators have argued that insulin resistance per se cannot produce hypertension because of the paucity of elevated blood pressure in certain populations in which obesity and insulin resistance are highly prevalent (e.g. Pima Indians, Mexican Americans, and Pacific Islanders). This argument does not rule out the possibility that insulin resistance contributes to hypertension only when it acts upon a susceptible substrate, i.e., in people who are already predisposed to hypertension. Thus, insulin resistance may cause only a moderate rise in blood pressure but not categorical hypertension. The latter may require genetic polymorphisms that favor development of hypertension. Unfortunately, the genetics of essential hypertension are poorly understood. Table 8 lists possible genes or pathways involved in the etiology of hypertension, but until specific causes have been elucidated, it will be impossible to determine how they respond to a state of insulin resistance. Nonetheless, the observation that nonobese, hypertensive patients often manifest insulin resistance is highly suggestive that primary insulin resistance contributes to hypertension.

Table 8

CANDIDATE GENES
FOR HYPERTENSION

- Renin
- Angiotension converting enzyme
- Angiotensinogen
- Atrial natriuretic peptide receptor
- α_1 Na,K-ATPase
- S_A gene
- Na-H antiporter
- Kallikrein

SUMMARY

Clustering of cardiovascular risk factors appears to be relatively common, and it confers a high risk for CHD. Abnormalities in the regulation of lipid and glucose metabolism and in blood pressure frequently coexist in single individuals, and together constitute the metabolic syndrome. These changes may be present as categorical abnormalities or as subclinical alterations. In either case the risk for CVD is increased, albeit to different degrees. In most patients, the metabolic syndrome likely is multifactorial in origin but in some patients single causes may predominate. The most intriguing hypothesis is that primary insulin resistance underlies the complete syndrome in some people. Several lines of suggestive data support this concept, but the common occurrence of primary insulin resistance as a cause of the metabolic syndrome has not been documented with certainty. Nonetheless, if true, the hypothesis holds so much potential for control of risk factors that it deserves continuing investigation.

A more direct connection with the metabolic syndrome can be made with secondary forms of insulin resistance, namely, obesity and lack of physical activity. Strong data support the concept that obesity in particular contributes to dyslipidemia, glucose intolerance, and hypertension. Whether these contributions are mediated through insulin resistance or other mechanisms have not been determined with certainty. Closely related to obesity is the issue of physical activity. Many reports indicate that regular physical activity can mitigate the metabolic syndrome. It can reduce insulin resistance and improve glucose tolerance; it can reduce plasma triglycerides and raise HDL-cholesterol levels; and in some patients it can lower the blood pressure. These beneficial effects of exercise may be enhanced over a lifetime. Thus, a lack of physical activity must be considered a secondary cause of the metabolic syndrome.

Another provocative issue is whether the diet, independent of obesity, has general or specific adverse effects on the metabolic triad. Certainly high intakes of saturated fat and cholesterol raise the total cholesterol level and lay the foundation for the adverse consequences of other components of the syndrome. Seemingly however their harmful actions do not go beyond raising LDL-cholesterol levels. Of increasing concern is whether high-carbohydrate diets have adverse metabolic consequences. Our data indicate that these diets do not increase insulin resistance, compared to diets high in unsaturated fat; however, they have metabolic similarities to insulin resistance in that they stimulate insulin secretion and raise 24-hour glucose levels. High-carbohydrate diets further raise triglycerides and lower HDL-cholesterol levels, another characteristic of the metabolic triad. Whether a high-carbohydrate diet adversely affects blood pressure has not been adequately studied. Finally, a high-salt intake can raise the blood pressure in salt-sensitive individuals, and thus likewise may simulate the action of high levels of insulin to cause sodium retention. The possibility needs to be investigated that salt sensitivity in some way may be related to insulin sensitivity.

Another factor that must be considered is aging. The prevalence of the metabolic syndrome certainly rises with age. What is it about the "aging process" therefore that predisposes to this syndrome? According to our hypothesis (Figure 11), two factors, either alone or in combination, may be at work. First, insulin sensitivity declines in older people, although this change may be secondary to a change in body mass and composition, i.e. an increase in body fat and a decrease in muscle mass. And second, aging may be accompanied by a decline in overall metabolic efficiency that acts independently of insulin resistance to produce the metabolic triad. Finally, aging could lead to both types of abnormality which acting together accentuate development of the

metabolic syndrome (Figure 11).

Finally, genetic factors may alter the host's responses to the stress of insulin resistance. In some instances for regulation of glucose and lipid metabolism, pertinent genetic abnormalities have been identified. However, the frequencies of their contribution to the various components of the metabolic syndrome have not been fully elucidated. Even less is known about the genetic regulation of blood pressure, and hence the interaction between insulin resistance and with genetic polymorphism in causation of hypertension awaits further clarification.

Finally, the therapeutic approach to the metabolic syndrome must be considered. Five approaches can be visualized: (a) modification of the secondary causes of insulin resistance (i.e. obesity and lack of exercise) (Figure 13); (b) development of therapeutic agents that will produce a generalized decrease in insulin resistance (Figure 14); (c) reduction of high LDL-cholesterol levels which are at the core of the metabolic syndrome (Figure 15); and (d) management of specific risk factors by treatment of more distal causes of the syndrome (Figure 16), and (e) interruption of the effects of the risk factors at the level of the arterial wall (Figure 17). First, modification of secondary causes of insulin resistance is at the heart of the public health approach to reducing risk factors. Second, further research and development are needed to produce effective drugs which produce a generalized reduction in insulin resistance; metformin and triglytizone are two agents that may have some of the properties of such an agent. Third, reduction of LDL levels through use of HMG CoA reductase inhibitors (statins) promise therapeutic breakthrough in the prevention of coronary artery complications of the metabolic syndrome. And fourth, continued attention to control of each component of the syndrome will be

necessary because correction of specific genetic defects individually affecting glucose metabolism, lipid metabolism, and blood pressure will be required for many patients. And fifth, future studies in vascular biology may uncover new strategies for prevention of the atherogenic actions of the risk factors.

Figure 13. Treatment of the Metabolic Syndrome

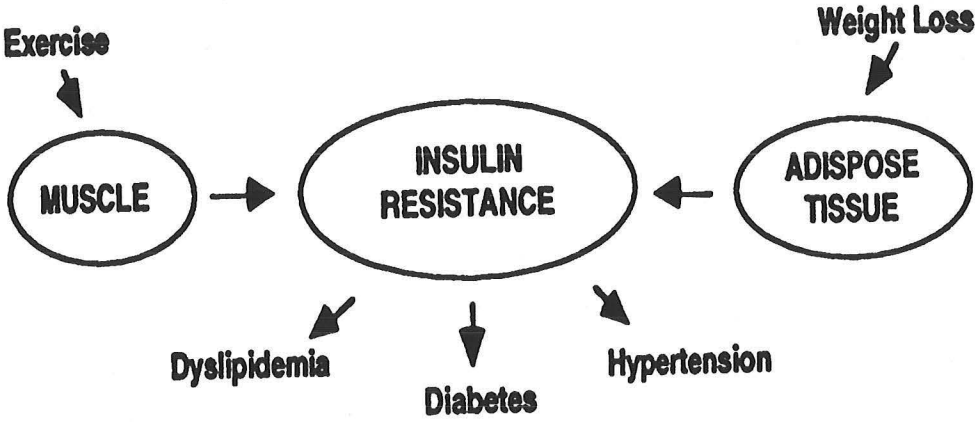


Figure 14. Treatment of the Metabolic Syndrome

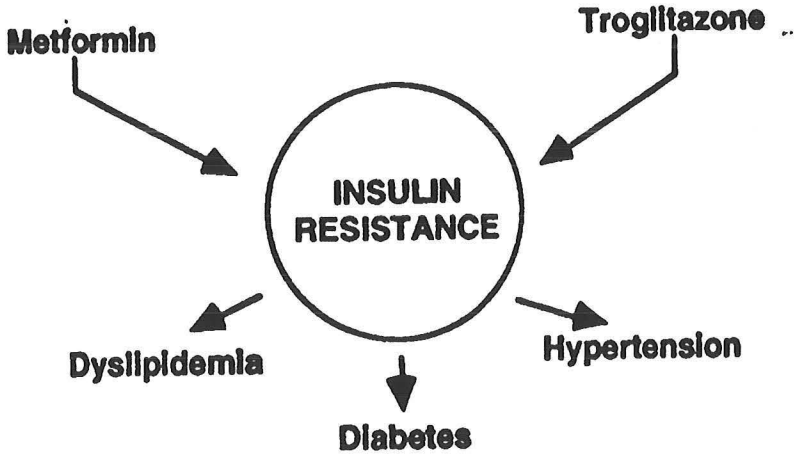


Figure 15. Treatment of
the Metabolic Syndrome

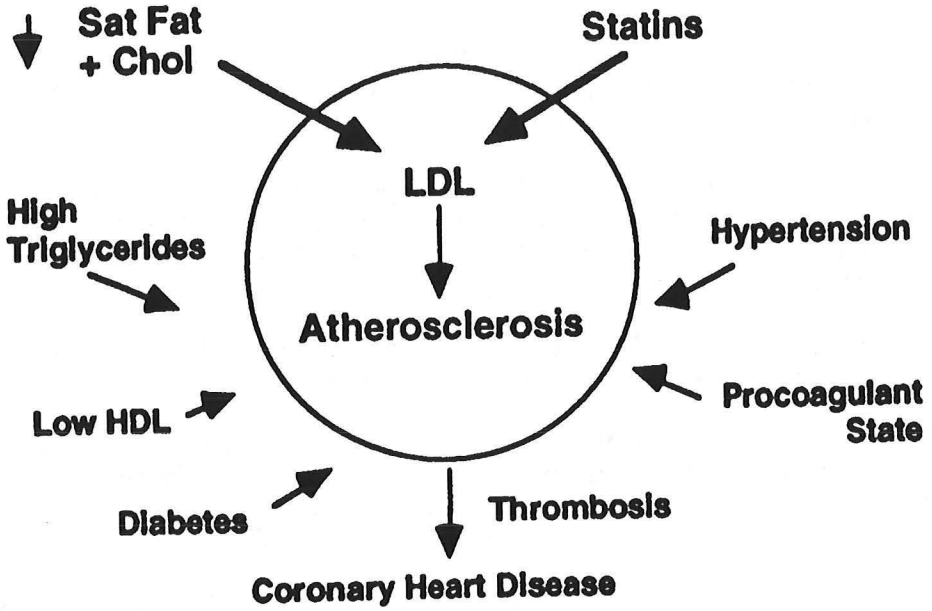


Figure 16. Treatment of
the Metabolic Syndrome

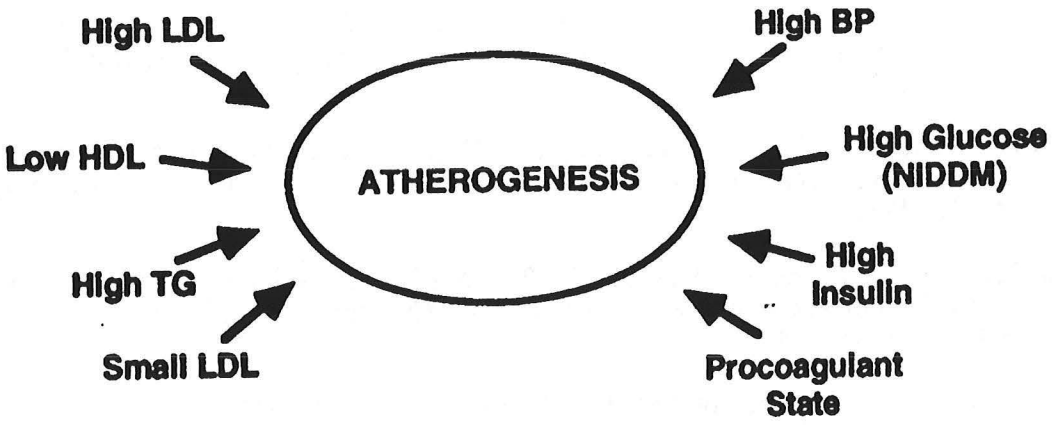
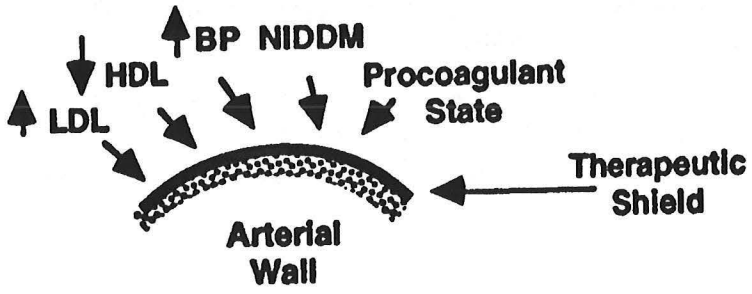


Figure 17. Treatment of
the Metabolic Syndrome



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