# METABOLIC AND HEALTH COMPLICATIONS OF OBESITY*

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January 26, 1989

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In many regions of the world, undernutrition continues to contribute to many health problems, notably to vitamin and protein deficiencies and infection. A major challenge for humanity is to provide adequate supplies of food for all the world's inhabitants. Already however many countries have ample food supplies, and as the cost of food declines another health problem - - overnutrition - - begins to emerge. Overnutrition can be defined as the consumption of more food energy than required to maintain optimal health. One of the most obvious manifestations of overnutrition is obesity - - the accumulation of excess body fat. Indeed, obesity is considered to be one of the major health problems of the United States and other affluent countries. Despite a "national" interest in health and fitness, the average body weight of Americans is increasing. Approximately 25% of the population, about 34 million Americans, are definitely overweight (MacMahon et al, 1987, Abraham and Johnson, 1980, Van Itallie, 1985). Another 25% have weights above the average, and many of these can be called mildly obese. Since most Americans can afford to eat as much as they desire, many are responding with an excess of adiposity. Only in the highest income group does the trend toward a high prevalence of obesity appear to be reversed.

Particularly alarming is the increase of obesity in American children and adolescents. During the past 15 years, the prevalence of obesity in both boys and girls, ages 6 to 18, has increased substantially (Dietz, 1985). The reasons for these striking changes are not clear, but they reflect a trend that portends a deterioration of health patterns among many Americans at a time when overall health should be improving.

Obesity is increasingly considered unaesthetic and even a social stigma; but beyond this, the consequences for health and disease are enormous. Many of the complications of overnutrition - - heart disease, high blood pressure, diabetes mellitus, and gallstones - - are well recognized. However, in spite of much research, the mechanisms by which obesity increases risk for these disorders are not well understood. Furthermore, overnutrition does not affect everyone in the same way. Some people are more likely to develop one complication, whereas others are subject to different complications; as a result, there is a variable susceptibility to the consequences of overnutrition. This variability may be determined by several factors, e.g. sex, age, race, and heredity. In fact, some people appear to be remarkably resistant to the potential complications of obesity; and for some, obesity may even confer an element of protection against certain diseases.

Physicians and nutritionists tend to view obesity with a uniformness that may be disadvantageous to individual patients. Certainly, the presence of obesity in a patient should alert the physicians to the possibility of several untoward medical consequences. The detection of these consequences may allow for a specific therapeutic intervention that may or may not be directed towards the underlying state of overnutrition. To appreciate this approach to the medical problems of the obese patient, it is necessary to consider the mechanisms by which overnutrition brings about unfavorable effects. For this consideration, three general principles must be outlined. These are the concepts of (a) inherent latent metabolic defects, (b) overnutrition vs. obesity, and (c) the metabolic consequences of overnutrition.

Inherent Latent Metabolic Defects

The notion of variability in predisposition to disease is well established in medicine. Accordingly, an individual may possess an underlying weakness that will not become manifest as clinical disease unless or until an adverse stimulus is applied. One such adverse stimulus can be overnutrition (or obesity). The underlying weakness can be called a "latent" metabolic defect, i.e. an abnormality that remains hidden until the individual comes under the influence of overnutrition. Such defects may reside in a variety of metabolic pathways, e.g. those of cholesterol, triglycerides, bile acids, apolipoproteins, glucose, insulin, uric acid, or electrolytes; because of this, the adverse consequences of overnutrition will for a given individual depend on which metabolic pathways are defective.

Overnutrition vs. Obesity

Overnutrition can be defined as the intake of more food energy than is required to maintain one's nutritional requirements and sustain a desirable body weight. One of the results of overnutrition is the accumulation of excess triglyceride in adipose tissue; in fact, obesity is perhaps the most obvious sign of overnutrition. Furthermore, the presence of excess adiposity may perpetuate the state of overnutrition because it serves as a ready supply of free fatty acids that are constantly being released into the circulation even when they are not required for normal metabolism. In a sense, an obese individual is constantly in a "hypermetabolic" state. This is reflected in part by the increased number of calories required to maintain constant body weight of obese individuals.

Recent studies on metabolic activity of adipose tissue in different anatomical locations in the body provides further evidence for a link between obesity and overnutrition. Several of the metabolic complications of obesity (e.g. hypertriglyceridemia, diabetes, and hypertension) appear to be closely tied to an excess of adipose tissue in the intraabdominal region (visceral obesity). The reason for this may be that visceral adipose tissue is more metabolically active than adipose tissue in other parts of the body; in other words it may more readily release its fatty acids into the bloodstream (Bolinder et al 1983; Goldrick and McLoughlin, 1970; Kisselbah et al, 1982; Bjorntorp, 1985). This response could be secondary to a decrease in insulin receptors on intraabdominal hepatocytes or to increases sensitivity of these fat cells to the action of epinephrinine (Beck-Neilson et al, 1976; Kissebah et al, 1982). The release of excess fatty acids may enhance the synthesis of triglyceride in the liver and reduce hepatic uptake of insulin (leading to peripheral hyperinsulinemia) (Seidell et al, 1987). Thus, excess intraabdominal fat could extend the effects of overnutrition into the fasting state.

A person does not have to be obviously obese to be in a state of overnutrition. Even a few pounds (e.g. 10 to 15 lbs) may be sufficient to provide an excess supply of free fatty acids to maintain an overnourished state. Evidence for this phenomenon is the elimination of a manifest metabolic abnormality (e.g. hypertriglyceridemia or hypertension) that often can occur with modest weight reduction. Thus, for many people, a body weight between the 50th to 75th percentile for given height and sex may deserve to be called "mild

obesity". An important principle not widely recognized is that the severity of complications of obesity may not be directly proportional to the degree of overweight but rather to the sensitivity of the individual to the state of overnutrition. In other words, mild obesity may be more detrimental to some people than marked obesity to others.

Recent data suggest that the metabolic state of an individual may be influenced to some extent by the composition of the diet. For instance, if one consumes an excess of calories as fat, he/she may preferentially store these extra calories in adipose tissue as triglycerides; in contrast, carbohydrates may be less "metabolically efficient" than fat, and thus may be more readily burned as energy (Dreon et al, 1988). The same may be true for alcohol and medium-chain fatty acids. However, this does not mean than an excess of nonfat calories is harmless; they can still put an individual into a state of overnutrition, and there will be metabolic consequences to pay. Further, if differenees in fates of fat and nonfat calories are proven to be real, it may be possible to be in a state of overnutrition and yet not become obese.

Metabolic Consequences of Overnutrition

As mentioned before, the most obvious result of overnutrition is the development of obesity. However, other metabolic consequences that are less obvious may still contribute to the complications of overnutrition. Some of these include an abnormally high synthesis rate of lipids (cholesterol, triglycerides, bile acids), increased secretion of insulin, and peripheral resistance to insulin action. Thus, the major hypothesis of this paper is that the metabolic effects of overnutrition combined with inherited "latent" metabolic defects are responsible for the complications of overnutrition. In the discussion to follow, the effects of overnutrition on the development of several diseases - - dyslipidemias, gallstones, diabetes mellitus, hypertension and cardiovascular disease, and neoplasm - - will be examined from the point of view of mechanism. A better understanding of the mechanism for these disorders may give clues to therapeutic modalities for their prevention.

## DYSLIPIDEMIAS

Hypertriglyceridemia

An elevation of serum triglycerides is common in many obese persons, but certainly not in all. Further, among those who are obese and hypertriglyceridemic, the severity of triglyceride elevation likewise varies greatly. In most overweight individuals having high triglyceride concentrations, caloric restriction will produce a definite reduction in serum triglycerides, indicating clearly that hypertriglyceridemia in obese patients is in some way related to obesity. We might therefore inquire into why obesity causes hypertriglyceridemia in some people but not in others. Most hypertriglyceridemic patients have an increase in serum concentration of very low density lipoproteins (VLDL)-triglycerides. Two mechanisms can be responsible for raised VLDL-triglycerides: (a) overproduction of VLDL-triglycerides, and/or (b) defective lipolysis of triglyceride-rich lipoproteins. Both types of abnormalities have been implicated in the pathogenesis of hypertriglyceridemia, and the role of each

can be considered.

Overproduction of VLDL-triglycerides. This abnormality has been postulated to occur on a genetic basis in the disorder called familial hypertriglyceridemia (Chait 1980). This condition may be characterized by a generalized overproduction of lipids by the liver, as suggested by the finding that patients with familial hypertriglyceridemia have increased synthesis of cholesterol and bile acids (Grundy et al 1987). Patients with primary hypertriglyceridemia often manifest a resistance to the peripheral action of insulin (Reaven, 1967, Kissebah et al 1976); this abnormality could contribute to the overproduction of lipids by the liver.

Defective lipolysis of triglyceride-rich lipoproteins. Dunn et al (1985) reported one family in which elevated triglyceride levels appeared to result from sluggish catabolism of VLDL-triglycerides. More recently, Sane and Nikkila (1988) reported that clearance capacities for triglycerides show patterns of variability along genetic lines. They postulated that an inherent variability of clearance capacities for VLDL-triglycerides is a major factor responsible for differences in serum triglyceride concentrations within the population. The mechanisms contributing to this variability in lipolytic capacity are unknown; whether defective lipolysis is related to differences in availability of lipoprotein lipase and/or hepatic triglyceride lipase, polymorphism in lipase structures, or apolipoprotein composition, has not been determined.

The recent findings of Sane and Nikkila (1988) are an extension of a previous hypothesis of Nikkila and Kekki (1971) which states that considerable polymorphism in clearance capacities for VLDL-triglycerides exists within a given population. On the basis of variability in profiles for production rates vs. serum concentrations of VLDL-triglycerides obtained in normotriglyceridemic subjects, we have proposed that many individuals have a "latent lipolytic defect" for VLDL-triglycerides (Grundy and Vega, 1982). When these people have relatively low production rates for VLDL-triglycerides, they will not develop hypertriglyceridemia, but should their production rates increase, their triglyceride concentration will rise into the abnormal range.

Effects of obesity on triglyceride metabolism. Our previous research further showed that overnutrition in obese patients induces an overproduction of VLDL-triglycerides (Grundy et al 1979). This effect has been reported by other investigators as well. A high production rate for VLDL-triglycerides is present in most obese subjects, even when they do not have overt hypertriglyceridemia (Grundy et al, 1979). Seemingly, many obese people are able to raise their clearance capacity for VLDL-triglycerides and thus avoid hypertriglyceridemia even when they have an excessive input of triglycerides into serum. In many people therefore overnutrition may enhance the synthesis of lipoprotein lipase to compensate for the overproduction of VLDL-triglycerides and thus avoid hypertriglyceridemia. Other obese patients in contrast develop hypertriglyceridemia in response to increased hepatic secretion of triglycerides. Seemingly, these patients fail to respond to overproduction of VLDL-triglycerides with a rise in lipolytic capacity. Since many of the latter people likely would not develop hypertriglyceridemia if they were not obese, we can surmise that they possess a latent lipolytic defect for triglyceride-rich lipoproteins. In accord, caloric restriction in these obese patients often will normalize triglyceride

levels (Wolf and Grundy, 1983); while their underlying lipolytic defect is not eliminated by caloric restriction, it remains hidden from view in the absence of overnutrition.

Hypercholesterolemia

Hypercholesterolemia usually is defined as an increase in serum LDL-cholesterol concentrations. Therefore, it may be worthwhile to review factors determining the concentrations of LDL cholesterol. LDL originates from the catabolism of VLDL remnants that in turn are the catabolic products of newly secreted VLDL. The rate of conversion of VLDL remnants to LDL thus is a factor determining LDL concentrations. Amounts of VLDL remnants converted to LDL are regulated by two factors: (a) rates of secretion of VLDL by the liver, and (b) the fraction of circulating VLDL remnants removed directly by the liver. These various rates can be traced by following the kinetics of VLDL-apo B-100, because every lipoprotein particle contains one molecule of apo B. Isotope kinetic studies have raised the possibility that LDL can be secreted directly by the liver, thereby bypassing VLDL, but recent evidence suggests that this apparent "direct input" of LDL represents merely a very rapid conversion of a subfraction of VLDL to LDL. A second major factor affecting serum concentrations of LDL is the rate of its clearance from the circulation. Most circulating LDL are removed by LDL receptors located on the surface of liver cells, although peripheral tissues also have LDL receptors and remove some LDL. The number of available LDL receptors in the body thus has a significant influence on serum LDL levels. Even though most LDL are removed by LDL receptors, a small fixed fraction of LDL is cleared by nonreceptor pathways; normally this latter route of removal however is not a major determinant of LDL concentrations. Hypercholesterolemia can result from abnormalities in either input or clearance of LDL. The role of these two mechanisms in the causation of hypercholesterolemia can be reviewed.

Defective clearance of LDL. The most dramatic cause of a decreased clearance of LDL is found in the condition called familial hypercholesterolemia (Goldstein and Brown, 1974, Brown and Goldstein, 1983). In this disorder, an inherited defect in the gene encoding for LDL receptors causes a deficiency of functional LDL receptors. Since one gene for LDL receptors is inherited from each parent, patients with heterozygous familial hypercholesterolemia have half the normal number of LDL receptors and twice normal levels of LDL-cholesterol. Another genetic disorder causing defective clearance of LDL is called familial defective apolipoprotein B-100 (Vega and Grundy, 1986; Innerarity et al, 1987). In this condition, the apo B-100 inherited from one parent is defective and does not bind to LDL-receptors; consequently, the clearance of LDL from the circulation is reduced, and LDL-cholesterol concentrations are increased.

Although these two monogenic disorders of LDL clearance are well defined, most patients with elevated levels of LDL do not have clearly identified genetic abnormalities; in general, the latter do not have as marked an elevation of LDL-cholesterol levels either. It has been postulated that most of them have a "polygenic" disorder (Goldstein et al 1973), but some could have less severe monogenic defects. Studies in our laboratory suggest that many of patients with primary moderate hypercholesterolemia have a reduced clearance of LDL from the circulation (Grundy and Vega 1985). Some of these could have less severe forms of familial defective apo B-100, but most probably have a reduced activity of

LDL receptors. Among the latter, an increased sensitivity to the action of dietary saturated fatty acids and cholesterol to suppress the activity of LDL receptors may be common. For example, we recently reported that some patients are unusually sensitive to dietary saturated fatty acids and develop clinical hypercholesterolemia only when saturated fatty acids are increased substantially in the diet (Grundy and Vega, 1988). Thus, the majority of people with hypercholesterolemia have a strong dietary component, and without the latter their abnormality would remain latent.

Increased influx of LDL. Another factor raising the LDL-cholesterol level appears to be an increased rate of conversion of VLDL to LDL. This abnormality could originate in two ways: (a) an increased secretion of VLDL into the circulation, or (b) a high fractional conversion of VLDL to LDL. A hypersecretion of VLDL-apo B has been postulated to be a major cause of the hypercholesterolemia in the genetic disorder called familial combined hyperlipidemia (Grundy et al 1987). The possible metabolic defect causing an overproduction of apo B-containing lipoproteins has not been determined, but variability in inherent rates of synthesis of hepatic apo B-100 may exist in the general population. Patients with familial combined hyperlipidemia often have an increase only in LDL levels, with serum triglycerides being normal.

The second reason for an increased influx of LDL could be a decrease in direct removal of VLDL remnants; such could have several causes. One of these is a reduced activity of LDL receptors, because VLDL remnants, like LDL, are removed by LDL receptors (Brown and Goldstein 1973). Another possible cause could be a reduced affinity of VLDL remnants for LDL receptors; this is known to occur with defects in the primary structure of apolipoprotein E, but other causes have not defined.

Mechanisms of obesity-induced hypercholesterolemia. Overnutrition can affect the metabolism of LDL in several ways. For example, a high consumption of total food energy in obese subjects seemingly causes an increased hepatic secretion of apo B-containing lipoproteins (Kesaniemi et al 1985; Egusa et al 1985). This response in turn leads to an increased conversion of VLDL to LDL, which can raise the LDL cholesterol level. In many obese subjects however the level of LDL cholesterol is not increased. There are at least two reasons for this. First, in obese subjects who are mildly hypertriglyceridemic, the cholesterol ester of LDL particles can be replaced by triglycerides, and because of this exchange reaction, the number of LDL particles in the circulation is increased, as revealed by an increase in LDL-apo B level, whereas LDL-cholesterol concentrations are not increased (Kesaniemi and Grundy 1983. And second, the activity of LDL receptors may be increased in many obese individuals, possibly the result of hyperinsulinemia.

When obesity is combined with milder forms of genetic hyperlipidemias, the combination can produce a distinct and even marked elevation of serum lipids. For example, in familial combined hyperlipidemia, increased serum lipids are not seen in childhood, but only in adults (Goldstein et al 1983). This uncovering of a latent defect with increasing age could be a result of the increasing adiposity. In fact, it was early recognized that obese patients from families affected with familial combined hyperlipidemia are particularly likely to manifest elevated plasma lipids. By the same token, if one has an inherent

suppression of LDL-receptor activity, because of excess consumption of saturated fatty acids and cholesterol or because of an inherited defect in receptor function, this person should be unusually sensitive to the effects of overnutrition and will more readily develop hypercholesterolemia.

An unresolved question is whether overnutrition contributes to the rise of LDL-cholesterol levels with age. In the United States, for example, the LDL-cholesterol increases by 30 to 50 mg/dl from early adulthood until later middle age (Heiss, et al, 1980). This rise undoubtedly contributes significantly to high risk for coronary heart disease in this country. Mechanisms responsible for this gradual but progressive increase in LDL levels with aging have not been determined. Studies from our laboratory (Grundy, et al, 1985) have shown that two factors - - an increasing production of LDL and a decreasing fractional clearance of LDL - - contribute to the increase. The former may be related to an enhanced input of apo B containing lipoproteins associated with overnutrition (Kesaniemi et al 1985; Egusa et al 1985). This change alone could cause a "saturation" of LDL receptors by increased quantities of LDL, and thereby reduce the fractional clearance of LDL; but alternatively, synthesis of LDL receptors may gradually decline with aging which likewise would reduce the fractional clearance of LDL.

The role of overnutrition in the "mass hypercholesterolemia" in the United States and other affluent countries thus is a subject of some dispute. On the basis of epidemiologic studies, many investigators believe that a high percentage of saturated fatty acids is mainly responsible for elevated LDL-cholesterol levels in the general population. The quantity as well as the quality of energy consumption may determine intakes of saturated fatty acids. If many people in our society are in a state of overnutrition, their absolute intakes of saturated fatty acids (and cholesterol) will be higher than revealed by analysis of diet composition; and the absolute intake of saturated fatty acids could have as much of an impact on cholesterol levels than the percentage intake. This "unrecognized" excess of cholesterol-raising saturates of fatty acids could promote suppression of LDL receptors (Spady and Dietschy, 1985). But beyond this mechanism, the overproduction of lipoproteins induced by a general state of overnutrition almost certainly is another factor raising cholesterol levels. Although epidemiologists usually emphasize diet composition in the causation of "mass hypercholesterolemia", a general overnutrition may be a major causative factor.

Hypoalphalipoproteinemia

Another major lipid risk factor is a low serum level of HDL-cholesterol. The reason why a low HDL level predisposes to an increased risk for coronary heart disease is unknown. Some workers believe that HDL promotes the removal of cholesterol from the arterial wall as part of its role in reverse cholesterol transport. Others speculate that decreased HDL levels are not directly atherogenic lipoproteins, such as VLDL remnants. Although the latter connection likely is real, it seems probable that reduced HDL levels in someway are directly atherogenic.

Mechanisms for reduced HDL levels. The origins of HDL are not fully understood. The liver and gut apparently secrete particles called "nascent" HDL;

these particles are disk-shaped lipoproteins containing apo A-I and apo A-II as well as phospholipids. They accept unesterified cholesterol from tissues and other lipoproteins; this cholesterol is esterified through the action of the enzyme lecithin-cholesterol acyl transferase (LCAT) which converts nascent HDL into small, spherical particles called HDL-3. Continuation of cholesterol-ester uptake leads to a larger species, HDL-2a. The latter transfers esterified cholesterol ester to VLDL in exchange for triglyceride; this transfer is catalyzed by cholesterol ester transfer protein (CETP), and transforms HDL-2a into the triglyceride-rich HDL-2b. Normally, only small quantities of HDL-2b actually circulate because its triglycerides are rapidly hydrolyzed by hepatic triglyceride lipase (HTGL), reconverting this species HDL-2b into HDL-3. The cholesterol ester transferred to VLDL makes its way back to the liver as VLDL degradation products - - VLDL remnants and LDL. Finally, it is likely that the various species of HDL can be partially removed by the liver and other tissues.

Several general mechanisms can be visualized for reduced HDL-cholesterol concentrations. First, there could be insufficient synthesis of HDL apolipoproteins (apo A-I and apo A-II) by the liver or gut. Genetic disorders have been found in which the synthesis of apo A-I is defective, and these are associated with reduced HDL-cholesterol concentrations. Second, an increased uptake of whole HDL particles could remove them from the circulation and reduce their concentrations. The most extreme example of this mechanism is found in Tangiers disease in which markedly enhanced catabolism of HDL is responsible for severe hypoalphalipoproteinemia. Increased removal of HDL particles may occur via the liver or extrahepatic tissues. Third, apo A-I can be transferred to VLDL, and if the VLDL concentration is high or if flux of VLDL is increased, this may drain apo A-I away from the HDL fraction. And fourth, in the exchange of triglycerides and cholesterol esters between VLDL and HDL, cholesterol ester can be lost from HDL; in hypertriglyceridemic states the magnitude of this exchange is enhanced resulting in a fall in HDL-cholesterol concentrations.

Effects of obesity on HDL levels. An inverse relationship between body weight and HDL-cholesterol concentrations is well established. People who are markedly overweight have HDL-cholesterol levels that are 8 to 10 mg/dl below the normal level (Wolf and Grundy, 1983). The precise mechanisms whereby overnutrition and/or obesity decreases HDL-cholesterol levels have not been determined. However, on the basis of the mechanisms discussed above, we might speculate about possible reasons for the fall in HDL-cholesterol levels in obese patients. It seems unlikely that overnutrition reduces the synthesis of apo A-I and apo A-II. The predominate mechanisms for HDL-cholesterol lowering probably relates to catabolism of HDL particles and/or apo A-I, or the triglyceride-cholesterol ester exchange. The hypertriglyceridemia commonly accompanying obesity may promote the transfer of apo A-I form HDL to VLDL, and thereby deplete HDL of apo A-I. It can also promote triglyceride-cholesterol ester exchange between VLDL and HDL. On the other hand, in weight-reduction studies in obese patients, we found that the HDL-cholesterol level does not rise immediately after starting caloric restriction even though triglyceride levels almost immediately fall to normal (Wolf and Grundy, 1983); this effect should have immediately stopped the depletion of apo A-I and cholesterol ester from HDL. Instead, only weeks later, after considerable weight was lost, did we note a slow but progressive increase in HDL-cholesterol concentrations. This observation suggests that an excess of adipose tissue, and not overnutrition alone,

contributes to the reduced HDL level; perhaps the excess of adipose tissue directly removes HDL particles from the circulation at an increased rate, and only when this excess tissue was eliminated did the HDL-cholesterol rise to normal.

## CHOLESTEROL GALLSTONES

Several factors have been identified as risk factors for cholesterol gallstones (Bennion and Grundy, 1978). These include the female sex, estrogenic hormones, pregnancy, certain hypolipidemic drugs (e.g. fibric acids), ileal disease, genetics (e.g. family aggregation, and race (e.g. American Indians). In addition, obesity appears to be a major risk factor for cholesterol gallstones. In some populations, approximately 50% of all gallstones can be ascribed to obesity (Marinovic, et al, 1972). The old adage "fat, forty, and female" gives a reasonably accurate picture of the epidemiology of gallstones. The question therefore is how does obesity contribute to gallstones. To understand the mechanisms involved, it is necessary to consider current concepts of the causation of gallstones.

### Pathogenesis of Cholesterol Gallstones

Two major abnormalities in bile composition are closely linked to development of cholesterol gallstones. These are supersaturated bile and nucleation of cholesterol to produce cholesterol crystals. Normally, biliary cholesterol is maintained in solution by its interaction with phospholipids and bile acids. One mechanism appears to be the solubilization of cholesterol in mixed micelles that contain bile acids and lecithin (Admirand and Small, 1968; Holzbach et al, 1973; Carey and Small, 1978). When amounts of cholesterol in bile exceed the quantity that can be held in stable solution, the bile is said to be supersaturated. Patients with supersaturated bile have been shown to be at increased risk for cholesterol gallstones. In recent years other mechanisms besides mixed micelles have been postulated to hold cholesterol in solution. These include lecithin-cholesterol complexes called liquid crystals and perhaps solubilizing proteins (Somjen and Gilat, 1983; Holzbach, 1984). The presence of these other systems may explain why many individuals with supersaturated bile do not develop cholesterol gallstones, but they do not negate the role of mixed micelles in maintaining cholesterol in solution.

The first mechanism described for production of supersaturated bile was a deficiency of bile acids in the enterohepatic circulation. This defect was noted initially in nonobese Caucasian men with cholesterol gallstones (Vlahcevic et al 1970), and it was then found in American Indians with cholesterol stones (Grundy, et al, 1972a). Seemingly, some gallstone patients do not secrete enough bile acids into bile to maintain cholesterol in solution. Rarely, a deficiency of bile acids can be the result of malabsorption of bile acids, as occurs with ideal disease (Heaton and Reed 1969); but more commonly, the abnormality appears to be due to a defect in feedback regulation of bile acid synthesis, i.e., the liver does not respond to a reduction in the quantity of bile acids in the enterohepatic circulation with a compensatory increase in bile acid synthesis (Grundy, et al, 1972a). Thus, the size of the bile acid pool is chronically maintained at a reduced level.

A second mechanism for an increased saturation of bile is an increased secretion of cholesterol in bile. All factors regulating biliary cholesterol outputs are not known, but estrogenic hormones appear to promote the secretion of cholesterol in bile (Kern et al, 1981, 1982). This finding may partly explain why women are more prone to gallstones than men. The fibric acids (e.g. clofibrate) also increase the biliary output of cholesterol (Grundy, et al, 1972b), but the mechanism is unknown. Whether undefined genetic disorders cause hypersecretion of cholesterol in bile has not been determined, but humans in general, in contrast to many other animal species, have a relatively high output of cholesterol into bile.

Another prerequisite for development of cholesterol gallstones is formation of cholesterol crystals (Sedaghat and Grundy, 1980; Holzbach, et al, 1984). Many people have supersaturated bile, either intermittently or continuously, and yet do not develop gallstones (Bennion and Grundy 1975). These people almost never have cholesterol crystals in their bile (Sedaghat and Grundy 1982). In contrast, those with cholesterol gallstones almost always demonstrate cholesterol crystals upon careful examination. The reason why some individuals are "crystal formers" while others are not has not been determined. The former may lack a critical protein that maintains cholesterol in solution, but this reason remains to be proven with certainty. In any case, the propensity to form cholesterol crystals combined with the presence of supersaturated bile usually leads to the development of cholesterol gallstones.

Role of Obesity in Cholesterol Gallstone Formation

Obesity is a powerful risk factor for the development of cholesterol gallstones (Bennion and Grundy 1978). It must be assumed that many people without gallstones have the potential for gallstone formation, but are protected by a lack of obesity. The major effect of obesity and overnutrition on biliary lipids is to enhance biliary secretion of cholesterol (Bennion and Grundy et al 1974, Mabee et al, 1976, Schaffer 1977). The increased output of cholesterol in bile is the result of an overproduction of cholesterol by the body; in fact, the synthesis of whole-body cholesterol is directly related to total body weight (Nestel et al 1969, Miettinen 1971, Nestel 1973).

Although obesity is almost universally produces an increase in biliary cholesterol, not all obese individuals develop cholesterol gallstones (Bennion and Grundy 1975). Apparently obesity must be present along with other factors before gallstones can develop. One of the latter defects may be a partial deficiency of bile acids in the enterohepatic circulation. A striking example of this mechanism is provided by the Pima Indians of Arizona who probably have the highest incidence of cholesterol gallstones in the world; approximately 80% of Pima women eventually develop gallstones, with the peak incidence in the twenties and thirties (Sampliner et al, 1970). Most Pima women are overweight, and as a result, they have an increased output of cholesterol in bile; but in addition, they have a defect in bile acid metabolism leading to a reduction in bile-acid pool sizes (Grundy et al 1972). This combination of an increased secretion of biliary cholesterol and a reduction in bile-acid secretion leads to highly supersaturated bile; it creates a highly unstable bile, and thereby greatly increases the likelihood of gallstone formation.

By the same token, if obesity is combined with a defect promoting nucleation of cholesterol in bile, the two should markedly enhance the risk for gallstones. In the absence of supersaturated bile, a nucleation defect may not necessarily lead to gallstone formation, but if this defect is combined with supersaturated bile, engendered by enhanced biliary outputs of cholesterol, gallstone formation is almost inevitable. This mechanism may be a common cause for gallstone formation in Caucasians in whom a deficiency of bile acids has been difficult to implicate as the causative factor (Mok et al, 1977).

## DIABETES MELLITUS

Most investigators and clinicians recognize a close linkage between obesity and noninsulin dependent diabetes mellitus (NIDDM). Approximately 70 to 80% of NIDDM patients are obese (West, 1983). Furthermore, a high percentage of markedly obese individuals (i.e. 40 to 60%) eventually will develop NIDDM (Salans 1987). It is conceivable that the metabolic abnormalities underlying NIDDM are likewise responsible for the development of obesity; but more likely, as most investigators believe, obesity independently contributes to the development of NIDDM. One view holds that obesity does not actually "cause" NIDDM but merely worsens it; another view however is that obesity is an intimate factor in development of persistent NIDDM; and in the absence of obesity, many individuals having NIDDM probably would never have developed it. In this section, these different possibilities and interrelationships can be considered in more detail.

### Metabolic Defects Underlying NIDDM

Many investigators hold that genetic factors contribute to the pathogenesis of NIDDM. If so, this implies that some individuals are genetically predisposed to NIDDM because of inherited metabolic defects. Abnormalities acquired with aging also may contribute to the tendency to develop NIDDM. Since NIDDM is essentially a syndrome characterized by elevations of plasma glucose, a number of metabolic defects theoretically could produce abnormally high glucose concentrations. These potential defects can be summarized in the following.

Peripheral insulin resistance. One abnormality contributing to NIDDM may be a resistance to the peripheral action of insulin. Several factors could be involved in the causation of insulin resistance. For example, the synthesis of insulin receptors could be deficient so that insulin receptor activity would be inadequate to meet tissue needs for uptake of glucose. When insulin receptors were first discovered, this potential mechanism generated considerable enthusiasm as a possible explanation for peripheral insulin resistance. In support, patients who have autoantibodies directed toward the insulin receptor manifest a clinical condition of severe insulin resistance. On the other hand, careful study of insulin receptors in NIDDM patients have revealed no consistent abnormality in their potential for synthesis; instead, their number can be reduced in hyperinsulinemic states by down regulation (Bar et al 1979). Therefore, most investigators now doubt that a defect in a patient's inherent capacity to synthesize insulin receptors is a major cause of insulin resistance in NIDDM.

A more likely mechanism for insulin resistance in the view of most is a

post receptor defect in glucose utilization that interferes with glucose uptake by muscle cells. Several types of post receptor defects can be visualized. First, an abnormality could occur in the storage of glucose as glycogen during postprandial hyperglycemia; this defect could produce a worsening of glucose tolerance, although it probably could not account for persistent hyperglycemia. The defect in glucose storage could reside in the enzyme, glycogen synthetase (Lillioja and Borgardus, 1988). And second, the basic post receptor abnormality for insulin resistance could reside in glucose oxidation. Such an abnormality might be secondary to a deficiency in key enzymes involved in glucose oxidation. This could occur on a genetic basis. A contributing factor could be competition between oxidation of fatty acids and glucose - - the so-called Randle effect (Randle et al, 1964, 1965). If muscle cells were to preferentially oxidize fatty acids, for a variety of reasons, this could be done at the expense of glucose oxidation.

Finally, insulin resistance might occur from an abnormality in the physical structure of muscle. Certain types of muscle fibers may be more sensitive to glucose utilization than others, and the relative proportions of different types of muscle fibers may determine rates of glucose oxidation. Furthermore, the availability of capillaries to muscle fibers could affect amounts of glucose available to muscle cells; if so, a reduction in the capillary network in skeletal muscle has been reported in patients with NIDDM (Lillioja and Borgardus, 1988).

Deficient insulin secretion. Another abnormality that may contribute to the hyperglycemia of NIDDM is a defect in secretion of insulin by pancreatic beta-cells (DeFronzo and Ferrannini, 1982). Although obese patients with NIDDM frequently have hyperinsulinemia, they seemingly produce insufficient insulin to meet requirements for glucose disposal (Halter et al 1979, Ward et al 1984). In many individuals with more severe forms of NIDDM, insulin levels often are clearly decreased, which adds further support for an insulin secretory defect (Bogardus et al, 1984). A genetic defect in the primary structure of insulin has been recognized in rare families with NIDDM (Given, BD et al 1980 Shoelson et al, 1983); this disorder illustrates the fact that abnormalities in insulin metabolism can underlie NIDDM. Thus, it is possible and even probable that many other individuals with NIDDM likewise may have quantitative or qualitative abnormalities in insulin secretion.

The nature of the underlying defect in insulin secretion in diabetic patients has yet to be determined. The beta-cell defect in NIDDM patients almost certainly is different from that of those with type 1 IDDM; former appears to be a very slowly progressive impairment of function of pancreatic beta cells. Conceivably a variety of disease processes could affect the beta-cells that would interfere with their ability to secrete insulin. Recently an amyloid-like protein has been found to be deposited in pancreatic islets of many patients with NIDDM (Westermark et al 1987, Clark et al 1987, Cooper et al, 1988); and the presence of this protein in some way may interfere with the secretion of insulin.

Hepatic glucose overproduction. Another possible source of excess plasma glucose could be an overproduction of glucose by the liver. Hepatic glucose is the product of gluconeogenesis, and it can be derived from amino acids and "three-carbon fragments" (pyruvate and lactate). Patients with NIDDM have been

found to have an overproduction of hepatic glucose (Glauber et al 1987); whether this overproduction is primary or is merely secondary to a state of peripheral resistance to insulin is not clear at the present time (Ferrannini et al, 1983).

Finally, in some patients with NIDDM, a single defect may affect several systems regulating the serum glucose level. For instance, a single defect, such as a deficiency of glucose transport units, might produce resistance to glucose in both peripheral tissues and islet beta-cells. In peripheral tissues the defect could retard peripheral utilization of glucose, whereas in the beta cell, it could retard the secretion of insulin. The net result of both would be to raise the plasma glucose concentration.

Although early investigators generally sought for a single defect to account for NIDDM, it is probable that a host of different abnormalities are responsible for the development of hyperglycemia. Indeed, several defects might occur simultaneously in one individual to raise the glucose concentration. Since serum plasma glucose levels are controlled at many different steps in glucose metabolism, abnormalities at any of these steps theoretically could produce glucose intolerance or fasting hyperglycemia.

Role of Overnutrition in Clinical NIDDM

An excessive intake of total calories, leading to obesity, may have several adverse effects on glucose regulation. Individuals who are genetically prone to developing NIDDM are already in a precarious metabolic state, and the presence of overnutrition may tip the balance towards overt diabetes. In the following discussion, the different sites at which overnutrition may effect an already compromised host can be considered.

Peripheral insulin resistance. Although many individuals may have peripheral insulin resistance on the basis of a genetic defect in glucose metabolism, resistance may be worsened in the presence of overnutrition. Several studies have shown that obese individuals have increased insulin resistance, even when they do not have abnormal glucose tolerance (Rabinovitz et al 1962, Kolterman et al 1980, Prager et al, 1986, Hissin et al, 1982, Bogardus et al, 1985, Meylan et al, 1987). An increased resistance to insulin action due to obesity per se is not universally accepted to exist (Hollenbeck et al 1984), but most studies are highly suggestive. It has been shown that obese adipocytes are insulin resistant (Salans et al, 1968), and this might contribute to generalized resistance in vivo, but at present, the current view holds that the insulin resistance of obesity resides mainly in muscle (DeFronzo et al 1985).

The means whereby overnutrition induces insulin resistance in muscle are not fully understood. Obviously, if carbohydrate availability exceeds the needs of muscles for its normal metabolism, they might be "relatively" resistant to glucose uptake even when rates of glucose utilization are normal. In addition, in the obese state, muscle may be absolutely resistant to uptake of circulating glucose. Obese people usually have an increased lean body mass, which means that they have an increased muscle mass (Egusa et al 1985). However, the extra muscle contained in the increase in lean body mass may not be normal in function and thus could be "resistant" to the action of insulin. Furthermore, many obese

people do not exercise sufficiently, and their "underexercised" muscle mass may be insulin resistant. Furthermore, obese people tend to have an increased flux of plasma free fatty acids (FFA) - - derived from the diet, excess adipose tissue, or increased catabolism of VLDL-triglycerides; this excess FFA may be utilized by muscle at the expense of glucose. This latter phenomenon, called the Randle effect, may contribute to peripheral insulin resistance of overnutrition (Randle et al, 1964, 1965, Felber and Vannotti 1964, Ruderman et al, 1969). Finally, persistent hyperinsulinemia associated with obesity may downregulate peripheral insulin receptors, thus promoting the state of insulin resistance (Bar et al 1979).

Substrate overload. Overnutrition is characterized by an unnecessarily high intake of total substrate, mostly carbohydrate and fat. From a simplistic point of view, the metabolic effects of overnutrition could reside entirely in the realm of lipids. An intake of energy exceeding requirements will of course produce obesity, but if the body were to be perfectly efficient, the only metabolic consequences of an excessive energy intake would be an expansion the adipose tissue mass. This extra adipose tissue in turn would be inert metabolically, i.e. fatty acids would be stored until they are needed to meet the demands of increased exercise or reduced caloric intake at a later time. In some species, and probably in some humans, this highly-efficient metabolic state may pertain, and when it does, there should be no deleterious effects of excess energy intake other than increasing the size of the adipose tissue fat pool. The metabolism of healthy young people may closely approach this idealized state, and young people often can tolerate moderate obesity without having obviously adverse effects. In such people, glucose disposal rates will remain completely normal.

However, in individuals who possess latent defects in peripheral glucose utilization, substrate overload can lead to an abnormality in glucose tolerance. For example, the Randle effect, induced by excessive dietary fatty acids, can worsen glucose tolerance, and down regulation of insulin receptors, secondary to excess dietary carbohydrate and hyperinsulinemia, can contribute to hyperglycemia. This overload phenomenon may be particularly likely to promote hyperglycemia in obese people who ingest low-fat, high-carbohydrate diets (Garg, et al, 1988). The hyperglycemic response could be immediate from hyperabsorption of glucose or delayed because of gluconeogenesis from recycling of three-carbon fragments or excess dietary protein.

Insulin secretion. At first glance, it would appear that overnutrition should not interfere with the capacity of the beta-cell to secrete insulin; if anything, it should promote insulin secretion. However, a lack of deleterious effect of overnutrition cannot be ruled out with certainty. For example, Unger and Grundy (1985) have proposed that "hyperglycemia begets hyperglycemia", i.e. the presence of hyperglycemia impairs insulin secretion and thereby accentuates hyperglycemia. This relationship might have a reversible and an irreversible component. For example, a reduction of hyperglycemia induced by weight reduction may reverse a functional suppression of insulin secretion. On the other hand, hyperglycemia could produce an irreversible defect in insulin secretion, e.g. by glycosylation of key proteins in beta-cells or islets. If the latter pertains, the worsening of hyperglycemia by overnutrition could produce an irreversible deterioration of insulin secretion. Thus, Modan et al (1986) have

suggested that a prolonged period of obesity contributes to development of NIDDM and an irreversible decrease in insulin secretion response.

Another detrimental, long-term effect of overnutrition in NIDDM patients could be an acceleration in the development of macro- and microvascular complications of diabetes. For example, atherogenesis could be enhanced by the accentuation of diabetic dyslipidemia due to overnutrition; at the same time, microvascular disease could be increased by a worsening of hyperglycemia. In both examples, overnutrition of vascular complications in patients with NIDDM; therefore even if overnutrition does not necessarily underlie the development of NIDDM, it could greatly influence long-term prognosis.

These considerations indicate the complex interrelations between overnutrition and NIDDM. Other mechanisms than those outlined above may play a role in this interaction. Much of the controversy surrounding the nature of these interrelationships may lie in the heterogeneity of pathogenesis and progression of NIDDM. Most of these concepts however suggest that overnutrition in a patient with an underlying defect in glucose metabolism is disadvantageous, and they do not justify the view that overnutrition has little clinical significance in NIDDM patients. For many patients, overnutrition probably is a significant factor in the occurrence of diabetic complications.

## HYPERTENSION

### Pathophysiologic mechanisms of essential hypertension

Essential hypertension is one of the most common physiologic disorders encountered in medicine. It is a major contributor to cardiovascular disease - - coronary heart disease, heart failure, arrhythmia, stroke and peripheral vascular disease. The term "essential" implies that mechanisms responsible for hypertension are unknown, but in reality, much has been learned about the physiologic regulation of blood pressure in humans and abnormalities in this regulation leading to elevated blood pressure. The failure to identify a single cause of essential hypertension probably can be explained by the absence of a single cause. More likely, the etiology of essential hypertension is multifactorial. This concept can be taken in two ways. First, multiple abnormalities in blood pressure regulation may exist in a single individual to raise the blood pressure to the elevated range; or second, single but different defects may exist in a group of hypertensives to raise blood pressure levels. Several pathological abnormalities currently are thought to contribute to the etiology of essential hypertension. They have been postulated to occur in the nervous system, heart, kidneys, vasculature, and hormonal system. Since the regulation of blood pressure is a highly integrated system, abnormalities in one system will affect others. For example, an increased activity of the sympathetic nervous system can increase cardiac output, promote arteriolar vasoconstriction, and stimulate increased secretion of catecholamines and possibly renin. Nonetheless, it may be useful to consider the different systems regulating the blood pressure separately, and then to speculate on their possible interactions in the genesis of hypertension.

Neural factors. One phenomenon that probably contributes to the

development of essential hypertension is an increased activity of the sympathetic nervous system (Dustan 1987). Cardiovascular responses that suggest a sympathetic component to the genesis of hypertension are orthostatic increases in blood pressure (due to an increase in orthostatic total peripheral resistance) (Frohlich et al 1967), rapid heart rate (Julius 1976), and increased cardiac output (Ulrych et al 1969, Dustan et al 1981). There is evidence that some people are susceptible to a rise in blood pressure accompanying mental stress, and this is reflected by increased plasma level of norepinephrine (Nestel, 1969). Finally, enhanced activity of the sympathetic nervous system may promote sodium retention (Katholi et al 1980, Louis et al 1974). Thus, overactivity of the sympathetic nervous system may be one component of essential hypertension. This neural effect seemingly is most common in young adults with mild hypertension.

Renal-sodium mechanisms. The kidneys are thought by many to be the key organ regulating blood pressure by determining one's response to dietary sodium chloride. For example, Guyton et al (1972, 1974, 1977) have proposed that cardiac output is increased in response to renal retention of sodium, followed by autoregulatory changes leading eventually to an increase in peripheral resistance. The defect leading to sodium retention could be with the kidney, or could reside elsewhere with the kidneys being the target organ. Individuals having such a defect presumably would be "salt-sensitive". Although most people seemingly are not overly responsive to dietary salt (Luft and Weinberger, 1982), a subgroup of salt-sensitive people probably exist in whom a high-salt intake leads to hypertension (MacGregor, et al, 1982, Watt et al 1983,and Maxwell and Waks, 1987). The individuals may have a true renal defect in the excretion of sodium.

The renin-angiotensin-aldosterone system. The role of the renin-angiotensin-aldosterone system in the causation of essential hypertension is still a matter of conjecture (Re 1987). Certainly, in renovascular hypertension, the release of increased amounts of renin is the primary mechanism. The effectiveness of converting-enzyme inhibitors in treatment of essential hypertension attests to the potential role of angiotensin in the causation of hypertension (Case et al 1977). It has been reported that some patients with essential hypertension have high levels of angiotensin II (Tuck et al 1985).

Cardiovascular factors. In young adults with essential hypertension, the cardiac output is frequently increased and total peripheral resistance is normal (Dustan 1987, and Pickering 1986, Frohlich 1987). At least two factors can raise cardiac output, e.g. enhanced sympathetic nervous activity and increased intravascular volume. In older hypertensives, the picture usually is reversed; cardiac output is relatively normal, and total peripheral resistance is increased (Frohlich, 1971). One cause of increased peripheral resistance can be enhanced vascular tone; the latter may be secondary to stimuli arising outside the immediate cardiovascular system - - increased sympathetic activity, elevated plasma catecholamines, or increased circulating angiotensin II. On the other hand, there are several potential mechanisms whereby abnormalities in the vascular tree itself could increase the peripheral resistance (Pickering, 1986): these include a decrease in the number of arterioles with increasing age (Hutchins, 1974), hypertrophy of smooth muscle cells of arterioles (Folkow, 1982), altered sensitivity of the arteriolar wall to circulating vasaconstrictors (Meier, 1981), increased permeability of smooth muscle cell membranes to sodium (Haddy 1983, Blaustein 1984), and increased blood viscosity. These possibilities

suggest that vascular tone is under a variety of influences that could be potentially abnormal in some patients and thereby predispose to hypertension.

Insulin resistance. Recently, there has been a growing interest in the connection between increased peripheral resistance to insulin action and hypertension. There appears to be a connection between hypertension and glucose intolerance in some patients, and several workers (Modan et al 1985, Lucas et al 1985, Christlieb et al, 1985 Manicardi et al 1986, and Ferrannini et al 1987) have suggested that the common link may be hyperinsulinemia. The latter may produce sodium retention by the kidney which could lead to expansion of plasma volume (DeFronzo, et al, 1976), or to hypertension by the mechanisms outlined above. Hyperinsulinemia might have other actions, such as to increase the activity of the sympathetic nervous system. Finally, the insulin-resistant state might adversely affect the distribution of intra- and extracellular potassium which also could promote vasoconstriction and raise the blood pressure.

Role of Overnutrition in the Causation of Hypertension

Without question, obese persons are more likely to be hypertensive than nonobese individuals. In younger adults (20 to 45 yrs), obesity imparts a 4 to 6 fold increase in risk for hypertension, whereas in those 45 to 75 years, the risk is approximately doubled (Van Itallie, 1985). Obesity appears to be a greater risk factor for hypertension in whites than in blacks in spite of the greater tendency of the latter to be hypertensive (Cornoni-Huntley, 1983). It has been estimated that 30% to 50% of hypertension in the U.S. population can be attributed to obesity (MacMahon et al 1987, and Tyroler et al 1974).

The rise of blood pressure with aging in the United States has been related to increasing adiposity with age because this phenomenon has not been observed in populations who do not show increasing obesity with age (Berchtold, 1981). Although increased body weight clearly is a risk factor for hypertension, it should be pointed out that not all obese individuals are hypertensive. This fact adds credence to the concept that a person must have a susceptibility to hypertension before it can be brought to light by overweight.

The exact "nutritional" factor associated with obesity that causes a rise in blood pressure has not been determined. For example, the strongest correlation between body weight and hypertension is found for lean body mass, and not excess adipose tissue per se (Forbes and Welle, 1983, Frohlich et al 1983). Furthermore, hypertension seemingly is more common in people with increased body-mass index than in people who have excess body fat but normal body-mass index (Schmieder and Messerli, 1987). On the other hand, the most common cause of increased lean body mass is an excess body fat because of enhanced stimulus to muscle growth imparted by the excess weight of adipose tissue. In addition, the presence of increased visceral adiposity has been implicated as a strong factor in causation of high blood pressure (Stine et al, 1975 and Blair et al, 1984, Lapidus et al, 1984, Larsson et al 1984); this effect on blood pressure may be directly related to visceral obesity per se. Finally, excess caloric intake per se cannot be ruled out as a contributing factor for hypertension. High energy intakes may be accompanied by increased ingestion of sodium chloride which can raise the blood pressure in salt-sensitive people; and excess calories can cause hyperinsulinemia, another putative cause of

hypertension. Thus, the link between obesity and hypertension may stem from several factors - - excess caloric intake, increased visceral adiposity, and greater lean body mass. Theoretically, overnutrition could raise the blood pressure either by increasing cardiac output or by raising total peripheral resistance. Both potential mechanisms can be examined.

Increased cardiac output. The major effect of the obesity state on the cardiovascular system is to increase the cardiac output (Messerli 1982; Schmieder and Messerli, 1987). Obese patients have an expanded intravascular volume which leads to increased stroke volume and heightened cardiac output. The higher intravascular volume may be related in part to an increased salt intake associated with higher caloric intakes. Messerli et al (1981) have reported that obese patients generally have an increased sodium excretion, which undoubtedly reflects a high salt intake. The hyperinsulinemia accompanying obesity may promote sodium retention; this too could raise the intravascular volume. Raison et al (1986) further reported that extracellular and interstitial fluid volumes are increased in obese men with hypertension; the increase in extracellular volume may be the result of an increase in lean body mass. Guyton (1977) believes that an increase in extracellular volume initiates a train of events leading to hypertension; the first step in this cascade is an increase in plasma volume.

The increased plasma volume of obese patients is translated hemodynamically into an increased cardiac output, which raises the arterial blood pressure; this appears to be a major mechanism whereby the obesity states produces or enhances hypertension. Obese patients with hypertension typically show myocardial hypertrophy and increase in cardiac muscle mass (Smith et al, 1933); and this hypertrophy is accompanied by cardiac dilatation, which increases the risk for congestive heart failure (Schmieder and Messerli, 1987). Left ventricular hypertrophy in obese hypertensives also may heighten the risk for sudden death, because of the predisposition of hypertrophied myocardium to arrhythmia (Messerli et al 1987). The latter danger could contribute to the "independence" of obesity as a risk factor for coronary mortality.

Whether obese hypertensives are less prone to coronary atherosclerosis and its consequences than nonobese hypertensives has not been resolved. Although a claim to this effect has been made (Barrett-Connor and Khaw, 1987; Cambien et al, 1985; Goldbourt et al, 1987), this claim is not substantiated in all studies (Bloom et al 1986); further, visceral obesity increases the risk for both hypertension and ischemic heart disease (Larsson et al 1984; Donahue et al 1987). On the other hand, obese hypertensives probably have less of an increase in peripheral resistance than nonobese hypertensives; (Lavie and Messerli, 1986; Schmieder and Messerli, 1987) and the former thus may have less arteriolar disease; if so they may be less prone to myocardial ischemia, nephrosclerosis, and cerebrovascular disease. Whereas obesity-associated hypertension may be less "malignant" than at the same level of blood pressure elevation in nonobese hypertensives, obesity-induced hypertension probably still increases the risk for end-organ disease, especially coronary heart disease, above that of normal blood pressure (Kuller 1987).

Increased peripheral resistance. It is unclear whether obesity (or overnutrition) raises total peripheral resistance besides increasing cardiac

output. This possibility although not demonstrated has not been excluded. For example, overfeeding has been reported to increase the activity of the sympathetic nervous system and to enhance the production of norepinephrine; the former-effect might be related to the activity of insulin to stimulate the insulin-sensitive area of the ventromedial nucleus of the hypothalamus (Sims and Berchtold, 1982). Obesity may raise renin levels, as suggested by the finding that renin levels fall with weight reduction (Tuck et al 1981). Excess salt intake and sodium retention in obese patients may raise peripheral vascular resistance in addition to its effects on cardiac outputs. Alternatively, insulin resistance may impair smooth muscle cell uptake of potassium which may increase vascular tone. Although all of these mechanisms are theoretically possible, it remains to be proven that obesity directly increases total peripheral vascular resistance. The increased cardiac output induced by obesity however could heighten blood pressure in an individual already having an increased peripheral resistance from another cause; this combination of effects may account for much of the hypertension found in obese individuals.

## CANCER

Overnutrition and obesity have been implicated as risk factors for several types of cancer. Those neoplasms most often cited as diet-related cancers are breast cancer, colon cancer, and prostrate cancer (Armstrong and Doll 1975; Snowdon, 1984). Evidence for a relation between diet and cancer is of two types - - epidemiologic and experimental. There are no clinical trial data to support the concept that modifying the diet will prevent cancer in human beings. Therefore, it remains to be established with certainty that dietary habits have a definite influence on the incidence of neoplasms in different societies. In humans, specific dietary factors that directly affect the development of cancer are a matter of dispute; however evidence related to the different factors can be reviewed.

Overnutrition (increased total energy intake). One concept holds that overnutrition in general - - regardless of the composition of the diet - - promotes the development of tumors. "Overnutrition" might be manifest as either obesity or increased body size; the latter implies "overnutrition" early in life. For example, there is a positive correlation between body size and the incidence of breast cancers between different countries (Willett 1987a; Gray et al 1979, DeWaard, 1975). Thus, the relatively low incidence of breast cancers in undeveloped countries, as compared to developed countries, may be related to early nutrition which determines body size later in life. If body size is the link between diet and breast cancer, this would mean that nutrition in childhood rather than later in life would be the crucial factor. Several studies (Lew and Garfinkel, 1979, Staszewski, 1977, Choi, et al, 1978, Brinton et al 1979; Paffenbarger et al 1980, Helmrich et al 1983), but not all (Willett, 1985) have suggested that obesity-associated increase in body weight is accompanied by an enhanced risk for breast cancer. Undoubtedly some of the increased body weight in these studies was due to excess adipose tissue, but lean body mass also may have been increased. Therefore, the link between body weight and breast cancer may not be mediated entirely through obesity.

Studies in laboratory animals are consistent with the concept of a relation

between overnutrition and cancer (Wolff, 1987). Certainly, semistarvation of laboratory animals delays the onset of spontaneous and induced neoplasms (White, 1961). Conversely, overnutrition often has the opposite effect, causing an earlier appearance of tumors (Wolff, 1987). This is illustrated by the earlier onset of spontaneous mammary carcinomas in obese virgin female C3H mice compared to nonobese mice (Waxler, 1953). As for humans, it is difficult to separate the effects of increased total body weight (or body size) and obesity per se. Nonetheless, in laboratory animals, overnutrition appears to cause an earlier onset in the development of tumors (Wolff, 1987). However, nutrition early in life seemingly is more important than obesity per se later in life for determining susceptibility to early-onset tumors.

Overnutrition apparently is less closely linked to colon cancer and prostrate cancer than to breast cancer. Even so, the American Cancer Society reported that cancer of the colon and rectum was increased significantly in males exceeding 30% of average body weight (Lew and Garfinkle, 1979). A similar result was reported for Seventh-Day Adventists, but not for other groups (Phillips and Snowdon 1985). Likewise, obesity was linked to increased risk for prostrate cancer among Seventh-Day Adventists (Snowdon et al 1984), but this relationship has not been confirmed in other populations.

The mechanisms whereby overnutrition may contribute to the development of premature cancer in humans, if in fact such occurs has not been determined. In the view of most workers, dietary factors are more likely to be a promoter of cancer than an initiator. This view seems consistent with the observation in laboratory animals that overnutrition causes an early onset of tumors rather than determining the absolute incidence. We might consider possible mechanisms whereby overnutrition might promote tumor development.

Dietary protein. If body size as determined by early growth and development is an important determinant of age of onset of tumors, then absolute protein intake early in life could be important. Although other dietary factors - - vitamins, minerals, and total energy consumption - - may contribute to early body development, protein intake could be important. Studies in laboratory animals support this possibility (Tannenbaum and Silverstone, 1949; Ross and Bras, 1973; and Wells et al 1976).

Total fat intake. The component of the diet most often implicated in the causation of cancer is an excess intake of fat. High-fat diets have been shown to reduce the latent period for the formation of tumors in mice and rats (Welsch, 1987). These diets have been shown to enhance tumor formation both in the initiation and promotion stages of tumor development (Welsch, 1987). Although the composition of the fat may be important, some investigators believe the a high percentage of total fat, regardless of type of fatty acids, promotes the development of cancer. Although high-fat diets tend to be high in total calories, several studies suggest that fat is different from other nutrients (i.e. carbohydrate and protein) in the induction of tumors in rodents. However, the mechanism whereby fatty acids of all types might be uniquely "co-carcinogenic" is not clear.

A connection between high-fat diets and human cancer has been proposed but not proven. When the prevalence of breast cancer in different populations is

plotted against dietary fat intake a positive correlation is found. Howe
a critical appraisal of the available evidence in humans by Goodwin and
(1987) failed to find convincing proof that percentage of dietary fat
causative factor in the development of breast cancer. Other recent studi
the United States have failed to find this connection (Willett, et al, 198
Jones, et al, 1987). Similarly, in spite of early enthusiasm for a link b
total fat intake and colon cancer, more recent investigations and review
revealed a doubtful connection.

Polyunsaturated fatty acids. Investigations in laboratory anima
provided stronger support for the concept that polyunsaturated fatt
(specifically linoleic acid) are more likely to be co-carcinogenic th
types of fatty acids (i.e. saturates and monounsaturates). Several me
have been proposed whereby polyunsaturated fatty acids might increas
risk. These have been reviewed by Welsch (1987). First, polyunsatu
suppress the immune system, which could allow for the development
(Hillyard, et al, 1979, Kollmorgen, et al, 1979, Wagner, et al, 1982)
polyunsaturates could increase membrane fluidity, which could pro
division (Lai, et al, 1980). Another possibility is that epoxides or
produced from polyunsaturated fatty acids may activate cell prolifera
et al, 1984). Similarly, an increased synthesis of prostagla
polyunsaturated fatty acids may be another activator of cell prolife
and Abraham, 1976, 1977). Finally, polyunsaturated fatty acids
"communications" between cells that could enhance their proliferati
et al, 1978). These various mechanisms are consistent with the
polyunsaturates are promoters of tumor development rather than in

A review of available data suggests that the diet, like ot
factors, may play a role in the development of cancer in humans. T
is consistent with both epidemiologic studies and investigations
animals. However, the precise mechanism (s) whereby d
carcinogenesis are by no means resolved. Most investigators are
that diet acts mainly in promotion and not in initiation of
Whether the crucial dietary factor is increased intake of total e
total fat, or polyunsaturated fatty acids remains to be determ

## CONCLUSIONS

This review reveals that obesity and the overnutrition
have profound effects on metabolism of several systems.
undoubtedly predispose to disease by worsening risk factor
dangerous when combined with underlying metabolic defects.
such defects, obesity may be relatively benign, and the unc
remain latent or hidden. In their presence, overnutrition
factor for determining whether a definite abnormality develo
produced. In one sense, overnutrition is a "provocative" te
an underlying metabolic defect. On the other hand, weight
a desirable body weight is reached, may not completely c
because of the underlying abnormality. It may be necessa
therapy to correct the latter. Therefore, it cannot be as
problem resides with obesity or overnutrition. While cor

be a major step in mitigating the problem, the underlying defect can persist, and it too may predispose to disease at a later date. Thus, the obese state may be useful for making an underlying defect clinically apparent, and the ultimate therapy may require correction of this defect as well as reducing body weight.

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