Diagnosis is a system of more or less accurate guessing in which the end-point achieved is a name. These names applied to disease come to assume the importance of specific entities, whereas they are for the most part no more than insecure and therefore temporary conceptions.

Sir Thomas Lewis
Reflections of Medical Education
The Lancet, 1944

I am indebted to my good friend Martin Sturman, M.D. (www.easydiagnosis.com) for furnishing this statement by one of the leading cardiologists of his day. Sir Thomas Lewis was largely responsible for the acceptance of the ECG as a clinical tool and his studies on "soldier's heart" in World War I led to his coining the term "effort syndrome". As noted above, he was also known for his criticism of diagnoses based on conjecture, and one can only wonder what his appraisal of metabolic syndrome might have been.

Metabolic syndrome is defined by the American Heart Association and the US National Heart, Lung, and Blood Institute as "multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease." These risk factors (such as abdominal obesity, hypertension, elevated blood sugar, lipid disturbances, increased proinflammatory and prothrombotic markers) are also strongly associated with the development of type 2 diabetes. Other terms that have been used to describe this disorder include Syndrome X, insulin resistance disorder, insulin resistance syndrome, pre-diabetes, dysmetabolic syndrome, plurimetabolic syndrome, central obesity syndrome, cardiometabolic syndrome, dyslipidemic hypertension, hypertriglyceridemic waist, and the deadly quartet. As a result, it is not hard to understand why definitions proposed by other groups differ.
The World Health Organization criteria require evidence of:

1. Insulin resistance (diabetes, impaired glucose tolerance, elevated fasting blood sugar)
2. At least two of the following
   a. hypertension (blood pressure greater than 140/90)
   b. dyslipidemia (high triglycerides or low HDL-cholesterol)
   c. central obesity (elevated waist–hip ratio or body mass index)
   d. increased albumin in the urine

The European Group for the Study of Insulin Resistance require insulin resistance (defined as the top 25% of the fasting insulin values among non-diabetic individuals) and two or more of the criteria noted above but not albumin in the urine.

The U. S. National Cholesterol Education Program Adult Treatment Panel definition, which is the one most commonly accepted here, is the even more liberal and requires only two of the following:

1. increased waist-hip ratio
2. elevated triglycerides
3. low HDL-cholesterol
4. blood pressure greater than 130/85
5. elevated fasting blood sugar

Discrepancies in these definitions as well as those proposed by others are due to differing opinions about the root causes of metabolic syndrome and how the disorder might best be prevented or treated. Some believe that obesity is the most important factor and that this leads to insulin resistance, which in turn increases deep abdominal fat deposits. This establishes a vicious cycle that results in accelerated atherosclerosis due to other risk factors as illustrated below.
Many insist that insulin resistance comes first and that the resultant obesity fuels subsequent factors such as inflammation that contribute to coronary heart disease. There is also growing evidence that inflammation could be the prime cause of coronary atherosclerosis both directly and via a cascade of responses that have a synergistic effect. In this scenario, the various components of metabolic syndrome are merely markers or sequelae of a complex metabolic derangement due to increased inflammation. There are criticisms that metabolic syndrome is being viewed as a disease rather than a collection of arbitrary risk factors that ignore the importance of homocysteine as a cause of inflammation and the role of nutrients like folic acid, vitamin C, selenium or magnesium. It has additionally been suggested that both metabolic syndrome and hypertension result from a derangement of the hypothalamic-pituitary adrenal axis due to stress. Superimposed on all of this is the undeniable but uncertain and variable influence of genetic factors on the development of hypertension, obesity, Type 2 diabetes and the various lipid disturbances that characterize metabolic syndrome. Many also argue that the term should be abandoned since it adds little to our present ability to predict or treat coronary heart disease.

The Evolution Of Metabolic Syndrome And Questions About Its Significance

Some insight into these differing views and why our assessment of its value is so controversial can be gained by a glimpse into the origins of metabolic syndrome. In 1956, Vague, a French physician, observed that diabetes, atherosclerosis, gout, and kidney stones were all associated with abdominal obesity and wondered if there might be some physiological connection. In 1967, Avogaro and Italian co-workers described six obese patients with diabetes, hypercholesterolemia, and very high triglycerides, all of which improved when they followed a low calorie-low carbohydrate diet. Ten years later, Haller first used the term "metabolic syndrome" in a German medical journal to refer to the association of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and fatty liver in discussing his theory about the additive effects of risk factors on atherosclerosis. A month or so later, an article in the same journal by Singer used metabolic syndrome to describe the frequency of obesity, gout, diabetes, and hypertension in patients with elevated lipoproteins. Also in 1977, Phillips, a New York endocrinologist, noted that risk factors for heart attack included elevated glucose, insulin, cholesterol, triglycerides as well as blood pressure. These formed what he called a "constellation of abnormalities" that were associated not only with coronary disease but also increased atherosclerosis, accelerated aging, and obesity. He proposed that there was some underlying factor that linked all of these risk factors that could lead to the prevention of cardiovascular disease and hypothesized that it was related to ovarian and testicular hormones.

However, our present use of the term metabolic syndrome stems entirely from Gerald Reaven's diabetes research at the Stanford University School of Medicine. In his 1988 Banting Award Lecture, he labeled the association of abdominal obesity, Type 2 diabetes and hypertension as "Syndrome X" and postulated that it was due to insulin resistance. It was an unfortunate choice that he would later come to regret since Syndrome X was widely hyped by the media as some new disease, few people understood what insulin resistance signified and Syndrome X had been used by cardiologists for well over a decade to describe something entirely different. The term "insulin resistance" was coined by Sir Harold Himsworth in 1936 to refer to a state in which giving a significant dosage of insulin produced a much less than expected biological response. During my residency training, it was arbitrarily defined as requiring at least 200 units of insulin daily to normalize blood glucose and prevent ketosis and we occasionally saw patients in the Johns Hopkins diabetes clinic who required much more than this. It was difficult to explain, although in retrospect, I believe that most were obese adult onset diabetics. In addition, "Syndrome X" referred to a condition first described in the 1970’s characterized by angina and an abnormal stress test but normal coronary arteries on angiography. It was not life threatening, more common in young women, and was sometimes called microvascular angina since it was often
associated with other vasospastic disorders like migraine and Raynaud's phenomenon. Because of the confusion created by media coverage of Reaven's syndrome X, it was renamed "Cardiovascular Syndrome X." "Broken heart syndrome" has recently been used to describe a variant that presents as an impending heart attack, also seen predominantly in young women, that has a favorable prognosis. It seems likely that these terms will be abandoned. As explained in an article published a few weeks ago, "The classic definition of cardiac Syndrome X seems inadequate both for clinical and research purposes and should be replaced with one aimed at including a sufficiently homogeneous group of patients with the common plausible pathophysiological mechanism of coronary microvascular dysfunction."

"Metabolic Syndrome X" was similarly used to differentiate Reaven's insulin resistant syndrome from the cardiac disorder, but the X was subsequently dropped, leaving us with metabolic syndrome. Many feel that this diagnosis will also disappear. Reaven believes that contemporary criteria are arbitrary and that it is a pathophysiological parameter rather than a diagnostic entity. As he noted in an article entitled The metabolic syndrome: requiescat in pace, "In conclusion, it appears that making the diagnosis of the metabolic syndrome does not bring with it much in the way of pathophysiologic understanding or clinical utility, and deciding that individuals do not have it because they fail to satisfy three of five arbitrarily chosen criteria may withhold relevant therapeutic intervention." Others agree. An article entitled The metabolic syndrome: an artificial and irrelevant notion pointed out that "A 'diagnosis' of 'metabolic syndrome' has no clinical or therapeutic relevance. It is better to treat each condition, if it is associated with an increased risk of cardiovascular disorders." Similarly, a joint 2005 statement issued by the American Diabetes Association and the European Association for the Study of Diabetes, The metabolic syndrome: time for a critical appraisal, concluded, "Our analysis indicates that too much critically important information is missing to warrant its designation as a 'syndrome'." CONCLUSION: Until much-needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the 'metabolic syndrome'." A few weeks ago, another joint statement was published with new guidelines for managing diabetes, prediabetes and cardiovascular disease. These advised that all patients with coronary disease whose diabetic status was unknown should have a glucose tolerance test. All diabetics should also be screened for coronary heart disease because both disorders occur together so often. In addition, since there may be no symptoms or signs, specialists in both disorders may not consider these strong links, especially since there may be no symptoms.

**What Causes Insulin Resistance And What Are Its Consequences?**

Quite by coincidence, it is likely that cardiovascular Syndrome X is also linked to Reaven's insulin resistance Syndrome X. However, the latter had nothing to do with Himsworth's insulin resistance that was based on the need to administer very large doses of insulin to control blood sugar. Insulin helps the body utilize blood glucose by binding with receptors on cell walls, much like a key fitting into a lock that opens a door. Once the door has been opened, glucose can enter the cell to provide energy or, in the case of muscle and liver cells, it can be stored for future use in the form of glycogen. Insulin resistance occurs when the amount of insulin normally available is insufficient to unlock and open all the doors causing the pancreas to keep secreting more. When cells resist and don't respond to these higher insulin levels, blood glucose becomes persistently elevated, resulting in type 2 diabetes. This happens in about one third of patients with insulin resistance but even diabetics whose blood sugars are controlled with oral medications have high insulin levels because of insulin resistance.

What causes insulin resistance has not been established although there are undoubtedly genetic influences that increase susceptibility to this as well as diabetes. There is mounting evidence that insulin resistance is also linked to increased stress and changes in lifestyles over
the past half century, particularly in the U.S. and other industrialized countries where economic status has improved. Obesity and physical inactivity aggravate insulin resistance and more and more of us are becoming obese and do not get enough exercise. Insulin resistance is characterized by increased levels of triglycerides and a reduction in HDL (good) cholesterol, both of which are associated with increased risk for heart disease. Almost all patients with type 2 diabetes and many with hypertension, obesity and coronary heart disease are insulin resistant. However, it is estimated that 20-25% of the healthy population without any of the above abnormalities may be insulin resistant since there are no diagnostic signs or symptoms. Many people with insulin resistance can produce enough insulin to maintain a normal blood sugar so it is necessary to perform a glucose tolerance test, during which insulin as well as blood glucose, is measured to detect whether the disorder is present. It is also not clear why some insulin resistant individuals develop diabetes while others do not, but maintaining a normal weight and exercising regularly help to prevent diabetes by reducing insulin resistance. **While governmental authorities and the American Heart Association advise a low-fat diet (less than 30 percent or even 20 percent of total calories) to prevent heart disease, this actually aggravates the adverse effects of insulin resistance as assessed by changes in blood lipids.** The recommended diet to reduce insulin resistance is one in which 40 percent of calories come from fats but limiting saturated fat to less than 10 percent of total calories. Many endocrinologists believe that such a low carbohydrate and relatively high fat diet is beneficial for patients with diabetes and/or obesity. Foods with a low glycemic index that do not result in a rapid rise in blood sugar may also be helpful. These include most fruits, vegetables and alcoholic beverages except for potatoes and beer. Two very recent papers suggest that calcium, vitamin D and magnesium supplementation can reduce insulin resistance.

The combination of insulin resistance and diabetes with high insulin levels is also linked with a variety of other problems that include the secretion of testosterone like steroids from the ovaries and adrenals. This association between disturbed carbohydrate metabolism and hyperandrogenism was first described in 1921 by Achard and Thiers, who called it "the diabetes of bearded women" (diabete des femmes a barbe). It was primarily seen in postmenopausal women who had diabetes, a deep masculine voice, excess hair (especially around the face), obesity and enlargement of the clitoris. In 1935, Stein and Leventhal described a syndrome characterized by a disturbed or absent menstrual cycle, infertility, hirsutism and enlarged ovaries containing multiple cysts with thickened capsules. It was usually diagnosed in women in their twenties or thirties who were seen because of fertility problems. Both of these disorders are considered to be variants of what is now called polycystic ovary syndrome, which is estimated to affect five to ten percent of women between late adolescence and the menopause. Polycystic ovary syndrome is associated with insulin resistance and high insulin levels that increase adrenergic activities and also stimulate the release of testosterone from the ovaries. Signs and symptoms due to androgenic effects include scanty or absent menstruation, infertility due to lack of ovulation, hirsutism, acne and obesity. Increased androgens also promote the development of fatty depots and an increased release of free fatty acids which, when transported to the liver, stimulate the production of triglycerides and the increased formation of low density lipoproteins that reduce HDL levels. **Polycystic ovary syndrome patients have at least seven times the risk of myocardial infarction compared to controls and up to 40 percent will have type 2 diabetes or evidence of impaired glucose tolerance by age forty.** Acanthosis nigricans is a skin disorder characterized by dark, thick, velvety skin in body folds and creases. While it can affect healthy people, it is often associated with obesity, diabetes and other endocrine disorders and most patients have high insulin levels due to insulin resistance. While it is possible that insulin resistance shares a common genetic origin with polycystic ovarian syndrome and acanthosis nigricans, many believe that it has a causative role. Up to half of all patients with essential hypertension also have insulin resistance and it seems likely that it will be found in other seemingly unrelated disorders.
Obesity, Insulin Resistance, Inflammation And Stress. Which Comes First?
It has been proposed that abdominal obesity causes insulin resistance, which in turn leads to inflammation, disturbances in carbohydrate and lipid metabolism, increased clotting tendencies, hypertension, endothelial dysfunction and the other metabolic syndrome abnormalities that contribute to accelerated atherosclerosis. However, as noted in the previous diagram illustrating this, obesity, insulin resistance, inflammation and some of these other factors have complex reciprocal relationships and it can be difficult to distinguish between cause and effect. If obesity is the primary problem, then perhaps faulty eating is at the root of insulin resistance and metabolic syndrome, as noted below.

The Development Of Systemic Insulin Resistance In Obesity-Induced Inflammation And Stress
From DeLuca C, Olefsky JM. (2006) Stressed out about obesity and insulin resistance. 
*Nature Medicine* 12, 41 - 42

In this scenario, overeating leads to the development of fatty tissue cells or adipocytes that secrete cytokines and other chemicals as well as free fatty acids that produce an inflammatory response. This results in localized insulin resistance and when these secretions reach liver and muscle tissue, they also increase insulin resistance at these sites. In addition to fatty tissue derived factors, stress induced inflammatory signals can arise independently within liver and muscle that similarly decrease sensitivity to insulin resulting in systemic insulin resistance. However, it is not overeating or obesity per se that is the culprit but rather what we eat and where excess fat is located. Obesity due to increased fat in the buttocks and extremities is quite different since there is evidence that this type of fat actually protects against atherosclerosis. A major contributor to abdominal obesity are fast foods containing trans fats that have been shown to increase insulin resistance. High corn syrup fructose beverages, which include most sweetened sodas and beverages, have been demonstrated to pile on pounds. It is not unusual for
children to consume two or three cans of soda daily and a 12 oz. can containing fructose corn syrup has the same number of calories as 10 tsp. of sugar. It's not hard to see how shoveling in 20, 30 or more teaspoons of sugar a day could cause problems and in one study, soda consumption was associated with an 80 percent increased risk for developing type 2 diabetes.

Deep visceral or abdominal obesity promotes inflammation and animal data suggest that inflammation is the link between insulin resistance and type 2 diabetes. This should not be confused with the classical definition of inflammation consisting of calor, rubor, dolor and tumor (heat, redness, pain and swelling). This type of inflammation is a chronic subclinical process unaccompanied by any symptoms or signs until it results in tissue damage. Its presence and degree of severity is usually assessed by acute phase reactants such as C-reactive protein (CRP) and/or alterations in interleukin-6, tumor necrosis factor and other cytokines. Since low-grade systemic inflammation correlates with almost all components of metabolic syndrome, often referred to as MS, some have suggested it should be renamed "systemic inflammatory metabolic syndrome" (SIMS), which would also avoid confusing it with multiple sclerosis, which is often referred as ms, but occasionally as MS.

Support comes from the Festa, et. al. study showing a close correlation between C-reactive protein (CRP) concentrations and the number of metabolic syndrome components that are present. Although CRP levels in patients with any one of these components can vary considerably, the progressive rise with each additional factor is quite clear. Whether the increase in this indicator of inflammation also predicts a correspondingly greater risk for coronary events remains to be seen. However, there is growing evidence that coronary atherosclerosis is an inflammatory condition as opposed to obstruction of blood flow due to lipid laden deposits. In some instances, inflammation may be due to infection with Chlamydia or other microorganisms. Chlamydia has been
cultured from atherosclerotic plaque and elevated CRP is also associated with this and other chronic infections.

Insulin dependent (type 1) diabetes is an autoimmune disease of the pancreas due to inflammation that results in a lack of insulin. Addison's disease, Graves' disease, Hashimoto's thyroiditis are inflammatory autoimmune diseases that affect the adrenal and thyroid. Autoimmune diseases result when the body's immune responses mistakenly attack its own tissues causing persistent inflammation and destruction. Other endocrine glands may be similarly affected and rheumatoid arthritis, lupus, regional ileitis and multiple sclerosis are also thought to be autoimmune diseases due to chronic inflammation. It is important to note that these may or may not be associated with increases in CRP and that there may be significant distinctions in what we refer to as inflammation. In addition, while CRP is not as variable as other acute phase reactants such as the sedimentation rate, levels are influenced by other factors and do not necessarily reflect the degree of inflammation.

As indicated previously and in prior Newsletters, many believe that the stresses associated with contemporary lifestyles are at the root of the current epidemic of obesity, type 2 diabetes and other manifestations of metabolic syndrome that raise the risk for coronary heart disease. Increased activity of the hypothalamic-pituitary-adrenal axis during stress results in a corresponding increase in cortisol secretion. Cortisol increases the deposition of deep visceral fat because it has a much higher concentration of cortisol receptors than other fat deposits. Cortisol also redistributes fat from other adipose tissue stores to visceral fat; possibly to allow the liver to have rapid access to fuel that might be needed for physical activity during stressful situations. Deep belly fat releases large amounts of free fatty acids into the portal circulation that continually stimulate the liver to produce glucose. Visceral fat cells also secrete large amounts IL-6 and other inflammatory cytokines that contribute to insulin resistance and there is a close correlation between increased abdominal fat and CRP levels. Adrenalin and other hormones secreted from the adrenal medulla during stress cause a breakdown of glycogen stores that also increase levels of blood sugar and fatty acids that further increase the demand for insulin. The above activities are normally inhibited by gonadal and growth hormones but the secretion of these is suppressed during stress.

Cortisol secretion is increased in Cushing's syndrome, a disorder that is associated with increased abdominal fat. Most cases of Cushing's syndrome are due to a pituitary tumor that produces excess amounts of ACTH, which stimulates the adrenal cortex to secrete cortisol. Following removal of the tumor, this excess abdominal fat diminishes or disappears as cortisol levels return to normal. Chronically stressed primates with high cortisol levels develop a corresponding increase in abdominal fat deposition. A study of middle-aged Swedish men similarly found that those with the highest levels of chronic stress also had the highest cortisol measurements and the greatest amount of deep belly fat. In one report, premenopausal women with greater amounts of abdominal obesity as assessed by WHR (waist to hip ratio) reported more chronic stress and had greater reactivity to stressful challenges compared to low WHR controls. In another, a high WHR in middle-aged men was associated with increased depression, anxiety, sleep disturbances and other stress related symptoms. (To calculate the WHR ratio, measure the waist at its narrowest point, usually just above the belly button and measure the hips around the widest part of the hip bones. Then divide the waist measurement by the hip measurement. A WHR of 0.8 or less for women and 0.95 or less for men is associated with good health that disappears progressively with higher ratios, especially in older individuals.) Obesity due to stress and cortisol is not as apt to occur in younger people because of the protective effects of other steroids like testosterone, estrogen, and progesterone. It is after age 40, when these sex hormones begin to decline that we start to see what is often referred to as" middle aged spread". Stress can also contribute to abdominal obesity by influencing what and how much we eat, as well as how often and when.
The above is a depiction of the interrelationship of factors in metabolic syndrome that emphasizes the importance of lipid disturbances. This is consistent with current dogma that cholesterol or its components are the cause of coronary atherosclerosis as demonstrated in the following accompanying explanation:

The dyslipidemia associated with obesity is multi-factorial, and is frequently associated with a cluster of interrelated cardiovascular disease risk factors that has been designated the metabolic syndrome. Key features of this dyslipidemia include raised triglycerides, reduced HDL cholesterol, and increased numbers of small, dense LDL particles. Obesity is a critical determinant of this dyslipidemia, operating through a number of metabolic influences that include reduced insulin sensitivity and changes in fatty acid metabolism that are described subsequently. Variations in the nature and magnitude of the dyslipidemia are due to the interaction of genetic factors with environmental influences, most notably diet and physical activity, and possibly stress. (emphasis added)

In the previous diagrams shown, obesity also seems to lead to everything else but there is no indication as to what causes the deposition of deep abdominal fat. This illustration suggests diet, physical inactivity and possibly stress, presumably in that order of importance. Along with many others, I believe that stress is more important than any other single factor since it is more closely linked to abdominal obesity than anything else. It also contributes directly to hypertension, insulin resistance, inflammation, clotting tendencies, autonomic and endothelial dysfunction and has far more of an effect on cholesterol and blood lipids than either
diet or exercise, as neatly summarized by the diagram below and its accompanying legend.


Schematic representation of the interactions between stress, visceral obesity, and the metabolic syndrome or between the soul and metabolism. Chronic stressors in genetically susceptible individuals may have an important pathogenetic contribution to the development of visceral obesity and the metabolic syndrome. Moreover, expanding obesity, due to the capacity of adipocytes to express and secrete proinflammatory molecules that activate the acute-phase reaction and cause endothelial dysfunction, may act as an additional chronic stimulus to the activation of the hypothalamic-pituitary-adrenal axis, as well as an enhancer of insulin resistance and its cardiometabolic complications. Thus, a vicious cycle may develop, whereby stress-induced hypercortisolemia contributes to adipocyte accumulation and vice versa, while both feed into insulin resistance and low-grade smoldering inflammation and the development of the metabolic syndrome and its adverse sequelae. (emphasis added)

Further support comes from a rigorous study designed and funded by the NIH in over 100 patients with established, stable coronary heart disease who were randomly assigned to two groups. Group 1 was given instruction in transcendental meditation, which was practiced for
16 weeks while Group 2 received structured health education training during the same period to serve as controls. At the end of the study, the meditation group showed significant reduction in blood pressure, insulin resistance and stress related autonomic nervous system activity. These improvements in components of the metabolic syndrome were achieved without changes in body weight, medication or psychosocial variables. Heart rate variability (which many believe is the most accurate objective way to measure stress and risk for coronary events as well as sudden death) improved twice as much in the meditation group compared to controls.

Whether metabolic syndrome contributes anything to our ability to improve determining or reducing risk for coronary heart disease and whether this diagnosis will still be used five or ten years from now remains to be seen. The current recommendations to prevent or treat metabolic syndrome are to avoid obesity and a sedentary lifestyle, which are hardly novel. I have tried to indicate why reducing stress should be added, and preferably at the top of this list. As the astrophysicist Bernhard Haisch noted, "Advances are made by answering questions. Discoveries are made by questioning answers."

Meetings Of Interest

3rd Annual Executive Summit on Innovation and the Cost-Appropriateness of Behavioral Health and Wellness, July 12-13, 2007, Atlanta, GA. Learn How To:

Cut Toxic Stress Effects
Improve Employee Health & Wellness
Control Rising Health Costs
Improve Bottom Line & Productivity

www.worldcongress.com/bhw

8th Conference of the International Stress Management Association
July 9th to 13th, 2007, Montreal, Canada
"The Globalization of Stress: Is Your Stress Like My Stress?"

Workshops and cutting edge presentations by leading authorities.
Co-sponsored by ISMA-USA & BFE (Biofeedback Foundation of Europe)

www.bfe.org/events/ISMA8.pdf
Copyright of Health & Stress is the property of American Institute of Stress and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.