HEALTH AND STRESS

The Newsletter of
The American Institute of Stress

May 2002

STRESS, OBESITY, DIABETES AND THE DEADLY QUARTET

KEYWORDS: Diabetic complications (role of race, gender, anger), BMI, prediabetes, HPA axis, Chrousos, Peeke, menopot, Björntorp, NES, resistin, Glycemic Index

According to a recent survey, 80 percent of Americans aged 25 and older are now overweight compared to only 58 percent two decades ago. One in three adults are obese or greater than 20 percent overweight, more than double the rate in 1983. The Surgeon General has warned that obesity is reaching "epidemic proportions", poses as great a health hazard as cigarette smoking and could be responsible for as many as 300,000 premature deaths a year.

One important consequence of this obesity epidemic has been a concomitant explosion in Type 2 or non-insulin dependent diabetes. This disorder is usually referred to as "adult-onset" diabetes because it occurs primarily in people over the age of fifty and in most instances can be controlled with diet and/or oral medications. Type 1 diabetes, also called insulin dependent or childhood diabetes, requires daily injections of insulin and has traditionally been considered to be the only form of the disease that occurs in children and adolescents.

These distinctions have become blurred over the past two decades. Between 1990 and 1998, there was a 70 percent rise in Type 2 diabetes in the 30 to 39 year-old age group and a 40 percent rise in those aged 40 to 49 compared to only a 31 percent increase for 50 to 59 year-olds. Of particular concern is the alarming increase in very young age groups. **Twenty years ago, only 2 percent of new cases of Type 2 diabetes occurred in the 9 to 19 year-old age group. That figure has now skyrocketed to 30 to 50 percent.**

Many cases are not diagnosed since childhood diabetes not requiring daily insulin is still considered rare by most physicians. Early symptoms are apt to be attributed to something else and proper treatment is often delayed until the complaints become more severe and the disorder has progressed to a more advanced stage. This may put many kids at increased risk for serious medical problems later on. Diabetes is a major cause of heart disease, the leading cause of blindness, kidney failure and limb loss, and the sixth leading cause of death for U.S. adults.

ALSO INCLUDED IN THIS ISSUE

According to a past president of the American Diabetes Association "All of this is preventable if you control blood sugar, but in order to do that you have to know that the disease is present". He believes that adolescents not treated for elevated blood sugar will have eye, kidney, leg and/or heart problems in their thirties. However, factors other than blood sugar control can influence when various complications are likely to start and how severe they may be.

Is It Nature, Nurture Or Stress?

There is little doubt that the dramatic increased incidence of Type 2 diabetes is a consequence of the current obesity epidemic but why are some people affected more than others? Is it gluttony or genes? Individuals with a family history of diabetes might be expected to be at greater risk but neither this nor excessive food intake explains differences associated with race, ethnicity, gender or low socioeconomic status. American Indians, Afro-Americans, Asian Americans, and Latinos are particularly vulnerable

Diabetes affects 6% of men and 8% of women of African descent, rates that are nearly double those seen in whites. In one report, Afro-American boys and girls were 3.5 and 6.1 times respectively more likely to develop Type 2 diabetes when compared with Caucasian controls. African Americans with diabetes also experience higher rates of disabling complications such as blindness, amputation and kidney failure and death rates are 2.5 times higher than for their white diabetic counterparts. Diabetes poses a particular problem for black women. Of the close to 16 million people diagnosed with all forms of diabetes, more than half are women and over half of these are of African ancestry.

Black women over 55 are almost twice as likely as white women to develop diabetes. One reason for this may be that ninety-percent of Type 2 diabetes is associated with being overweight and more than two out of three black women fit this description. Almost 40 percent of this group are obese since they are 20 percent or more over their ideal body weight. A recent *New England Journal of Medicine* article devoted to Type 2 diabetes in females concluded that half of all cases could be prevented by proper diet, regular exercise, stopping cigarettes and avoiding excess alcohol consumption. However, much more may be required when it comes to black females.

As the president of the Black Women's Health Project, a Washington-based nonprofit organization, noted "In order to address this epidemic among black women, we must address psycho-social factors as well as diet and physical activity. We have to address issues around stress and body image. Black woman face lifestyle stressors where food means a lot more than nutrition. Food represents comfort and love, which makes it extremely difficult for many women to change lifestyle patterns." A specialist at the Joslin Diabetes Center in Boston also believes that "Many people use food to treat their depression."

Stress can contribute to the development and aggravation of diabetes via various pathways. Stress-related hormones like adrenaline and cortisol elevate the blood sugar by breaking down carbohydrate stores (glycolysis) or by metabolizing protein into glucose (gluconeogenesis). Stressed out diabetics may not take their medications as scheduled, skip meals or eat erratically and tend to snack more frequently when upset, particularly on sweet or greasy high calorie comfort foods.

However, stress may play a much more sinister and important role in Type 2 diabetes because it increases insulin resistance. Type 1 diabetes occurs when not enough insulin is produced due to destruction of pancreatic beta cells. Type 2 diabetes results not from any lack of insulin but rather a puzzling resistance to its effects, which can cause a cascade of metabolic and health problems.

The Metabolic Syndrome And Stress

The Metabolic Syndrome refers to a condition characterized by abdominal obesity, hypertension, elevated blood sugar and lipid abnormalities. It is not a specific metabolic disorder or disease but rather a cluster of components that have been recognized for at least 75 years under various names, including **Syndrome X, the Deadly Quartet, and the Insulin**

Resistance Syndrome. In an effort to be more specific, the NIH recently defined Metabolic Syndrome as being present when at least three of the following are found:

- A waist measuring 40 inches or more for men and at least 35 inches for women
- levels of triglycerides of 150 mg./100 cc. or higher
- HDL levels of less than 40 mgs. in men and less than 50 mgs. in women
- blood pressure of 135/80 or higher
- fasting blood sugar over 110 mg./100 cc.

Metabolic Syndrome is associated with an increased risk for diabetes, coronary heart disease and premature death that now affects more than one in five American adults. It is believed to result from a combination of genetic and lifestyle factors that include overeating and not enough exercise. What seems to connect these seemingly unrelated components is a reduced ability of insulin to transport glucose into cells and tissues to provide energy. The body attempts to overcome this resistance or insensitivity to insulin by increasing its production. Type 2 diabetes eventually results when the pancreas can't continue to maintain its increased production of insulin since blood sugar rises even though insulin levels are actually elevated.

The presence of any single component of this "Deadly Quartet" raises the risk of coronary heart disease and mortality significantly. However, when more than one coexist these risks are greatly magnified and are much more than would be anticipated from a simple additive effect. This is particularly true when other aggravating influences like heredity, smoking, sedentary lifestyle, aging and particularly stress are superimposed.

In one study designed to delineate the significance of different Metabolic Syndrome components for coronary disease, 3000 men were followed for over four years. The presence of diabetes or high blood pressure alone increased the risk of a heart attack by 2.5 times and when both were present the risk was increased 8 times. **When abnormal lipid levels were present together with high blood pressure and/or diabetes the risk of a heart attack was 20 times higher.**

Stress, and particularly feelings of anger, may also contribute to the development of this syndrome. In one study, 541 healthy pre-menopausal females aged 42-50 years were followed for approximately 11 years. **Of the 37 women who satisfied the criteria for Metabolic Syndrome on entry, all scored high on anger measurement scales.** In addition, each of the 96 women who subsequently developed the syndrome also showed increasing anger measurement scores during the course of the study in contrast to controls who showed no rise. Researchers also found that women who had experienced a progressive decline in social support over the duration of the study were twice as likely to eventually develop Metabolic Syndrome compared to others in whom the degree of social support was stable.

Another study attempting to relate Type A traits in healthy young adults to the subsequent development of Metabolic Syndrome came to a similar conclusion. High Aggression-Hostility ratings and high anger scores had the greatest predictive power but how anger contributes to each of the components of this syndrome is not clear. A key factor appears to be the relationship of stressful emotions to the development of insulin resistance, as effects on blood pressure, blood sugar and lipid levels. It should be noted that, although not specifically mentioned, Metabolic Syndrome is also associated with a tendency to quicker coagulation and clot formation as well as the promotion of inflammatory responses. Both of these activities, which could favor the development of certain cardiovascular complications, are influenced by stress hormones.

Insulin Resistance And Syndrome X

Diabetes was originally thought to be due to a deficiency in the production of insulin. This is what happens in Type 1 diabetes when the insulin producing cells in the pancreas have been attacked and destroyed by the immune system. Type 1 diabetes tends to be inherited, usually surfaces during childhood and requires daily injections of insulin. Insulin resistance was initially arbitrarily defined as requiring more

than 200 units of insulin daily to control elevated blood sugar and prevent ketosis. Some patients required several times this amount because they developed antibodies to insulin that blocked its effects.

Insulin resistance as it is currently used is quite different and often occurs in the absence of diabetes. It is a metabolic disorder in which the normal ability of insulin to promote glucose uptake and utilization in cells is inhibited. Insulin resistance is closely linked to Metabolic Syndrome but all the connections are not clear. One factor appears to be an overloading of the tissues with lipids. Patients with insulin resistance usually have high levels of free fatty acids and when these enter muscle cells lipid overload occurs that induces insulin resistance. The body compensates by producing more insulin so that blood insulin levels are high. This helps to drive more glucose into the cells and also to prevent blood sugar levels from becoming too elevated. High blood insulin levels also suppress the release of fatty acids from adipose tissue.

As we get older our ability to produce insulin declines although there is a great deal of individual variation. When the production of insulin is no longer able to overcome insulin resistance, blood glucose levels become permanently elevated. The diagnosis of Type 2 diabetes signifies that fasting levels exceed 126 mg./100 cc. While there are many hormones that cause an increase in blood sugar, insulin is the only one that lowers it. Insulin also has other important metabolic activities. It promotes glycogen, fatty acid and protein synthesis, inhibits the release of fatty acids from adipose tissue and suppresses the production of apolipoproteins and other lipid factors.

The link between insulin resistance and compensatory hyperinsulinemia with hypertension, high triglycerides, low HDL and other risk factors for coronary heart disease was first noted in 1988 by Gerald Reaven. He suggested the term "Syndrome X" to emphasize the unknown nature of these relationships and their consequences. It is often called Metabolic Syndrome X to distinguish it from another Syndrome X used in 1973 to describe patients with angina-like chest pain and positive stress tests but no evidence of coronary artery disease on angiography. Quite by coincidence, many of these chest pain Syndrome X patients also show evidence of insulin resistance.

Metabolic Syndrome X is important because it has become increasingly prevalent in the U.S and Western society and is associated with an extremely high incidence of cardiovascular disease and premature death that can be prevented or significantly reduced with prompt and proper treatment. Unfortunately it is often unrecognized by patients as well as their physicians until complications occur. Since Reaven's original description, the list of coronary risk factors linked to Syndrome X has grown to include very low density lipoproteins (like apolipoprotein b), slower clearing of blood fats after meals and a decreased ability to break up clots or inhibit clot formation.

Insulin resistance is present in almost all patients with Type 2 diabetes and has likely existed for years before the onset of any signs or symptoms of diabetes. Studies show that microvascular complications of diabetes like retinopathy and neuropathy as well as accelerated atherosclerotic deposits in coronary and other arteries often begin many years prior to any diagnosis or suspicion of diabetes. While it is important to keep blood sugars within normal limits, many authorities now believe that the long term complications of diabetes are related more to the degree and duration of insulin resistance than poor blood sugar control. The scary thing is that insulin resistance can be demonstrated in about a third of the U.S. population, the vast majority of whom are completely unaware that they may be headed for Syndrome X troubles.

Obesity, Insulin Resistance And Stress

Obesity is the most common cause of Type 2 diabetes because it is associated with insulin resistance. Obesity is probably the most common cause of insulin resistance in others who do not have diabetes. It is important to emphasize that **individuals with evidence of increased insulin resistance are at greater risk for**

cardiovascular disease even if they are not obese or significantly overweight. In "*Syndrome X: Overcoming the Silent Killer That Can Give You a Heart Attack*," Reaven estimated that 25% of nondiabetic Americans also have insulin resistance and glucose metabolism problems, though most don't know it

You can determine if you have insulin resistance and some idea of its severity by measuring blood insulin levels in a fasting state and two hours after consuming 75 grams of glucose. Elevations over 15 mcIU after fasting or 50mcIU after glucose intake indicate increased insulin secretion due to insulin resistance. Another indicator of insulin resistance is obesity due to increased abdominal fat. There are various ways to measure this including electrical impedance, caliper measurements and CTT scans. Or you can simply measure the circumference of your waist and hip. A waist/hip ratio over 1 for men or greater than .88 for women indicates central obesity. The combination of marked abdominal obesity and an elevated BMI (body mass index) is even more strongly correlated with a greater degree of insulin resistance and its cardiac complications.

The easiest way to calculate your BMI to determine if you are overweight or obese is to start with your weight in pounds and your height in inches. To get your body mass index:

A) Multiply your weight by 703.
B) Multiply your height by your height.
C) Divide the answer to A by the answer to B and round off to the nearest whole number.

Thus if you are 5-foot-7 (67 inches) tall and weigh 140 pounds: A) 140 x 703 = 98,420. B) 67 x 67 = 4,489. C) 98,420 divided by 4,489 = BMI of 22. A BMI between 19-24 is healthy, 25-26 is overweight and values over this signify obesity and a progressively increased risk for diabetes and its complications.

Certain lipid levels can also be useful to screen for insulin resistance and compensatory hyperinsulinemia, since insulin decreases HDL and increases triglycerides. An elevated blood sugar is a red flag but the government now estimates **there are nearly 16 million Americans with what they have termed "pre-diabetes" who are also at significantly increased risk. These are mostly individuals 40 or older with a fasting blood sugar between 110 and 125** mg./dl. or from 140 to 199 mg./dl. 2 hours after drinking a glucose-rich beverage.

As indicated previously, obesity seems to be a major factor in the development of insulin resistance and its progression to Type 2 diabetes. Stress-induced eating can be a major contributor to obesity and increased secretion of adrenaline and cortisol may accelerate the development of insulin resistance. These stress-related hormones have effects on glucose metabolism that are the opposite of those of insulin. Obesity also leads to increased production of resistin, a hormone released by fat cells, that is specifically antagonistic to insulin.

Where you have that extra fat may be just as or even more important than how many extra pounds you are carrying. A pot belly is much more dangerous than having big buttocks and there is abundant evidence that stress can cause abdominal obesity. Patients with Cushing's syndrome due to a pituitary tumor have the deadly quartet of hypertension, lipid abnormalities, insulin resistance and compensatory hyper-insulinemia seen in Syndrome X. They also have central obesity due to increased secretion of cortisol. After the tumor is removed, cortisol levels return to normal and the excess abdominal fat tends to disappear.

Further support comes from studies in monkeys showing that when they were subjected to chronic stress there was a significant increase in abdominal fat deposits. Another report confirmed the relationship between worry, cortisol levels and abdominal fat in middle-aged men. Those with the highest stress levels also had the highest levels of cortisol and the most deep-belly fat. However, the stress-abdominal fat connection appears to be much stronger in perimenopausal women.

Toxic Stress And Visceral Obesity

In our June 2000 Newsletter (Is Stress Keeping You Fat?) I referred to a recent book entitled *Fight Fat After Forty* by Pamela Peeke, which has understandably become a best seller. She apparently became

interested in this topic while working at the National Institutes of Health with George Chrousos, a distinguished endocrinologist who has written extensively about stress and the hypothalamic-pituitary-adrenal (HPA) axis. In a 1995 article written with Chrousos entitled "Hypercortisolism and Obesity" Peeke emphasized that **increased deep abdominal fat is associated with the abnormalities seen in Metabolic Syndrome and a greater risk for cardiovascular disease than increased fat deposits in the buttocks**. She noted that central obesity and metabolic syndrome are also seen in Cushing's Syndrome and that both of these findings tended to disappear when the disorder was cured and cortisol levels returned to normal.

Peeke and Chrousos therefore speculated that chronic stress with its resultant increased cortisol levels might be expected to mimic what happens in Cushing's syndrome. Understanding how stress upsets normal hypothalamic-pituitary-adrenal axis relationships and its impact on other endocrine organs might provide insights into why and when abdominal obesity occurs that could have important implications with respect to both longevity and the quality of life. Subsequent studies suggest that their hunch was right on target.

Swedish researchers showed that stress related cortisol secretion in 51-year old men correlated not only with increased abdominal obesity but other endocrine, metabolic and hemodynamic abnormalities that might explain the cardiovascular complications associated with metabolic syndrome and stress. Peeke believes the problem is magnified in 40-60 year old females subjected to chronic stress who reach for candy, cookies, chips and other high-fat, high-carbohydrate foods to relieve their anxieties. They gain weight because the fat from those extra calories tends to be stored in the abdomen, where it is dangerous as well as unsightly.

The reason we develop "middle-aged spread" is that male and female sex hormones tend to protect against excessive buildup of abdominal fat in younger people. Levels of these hormones start to decline after age 40, when many women are also experiencing increased stress because of the need to deal with a defiant teenager, care for an aging parent, juggle work and other family responsibilities, menopausal symptoms, concerns about appearing less attractive, etc. Peeke refers to this as "toxic stress", as opposed to other daily hassles like getting stuck in a traffic jam. Toxic stress is associated with increased levels of hormones like cortisol that stimulate appetite, encourage nervous eating and increase the deposition of deep abdominal fat.

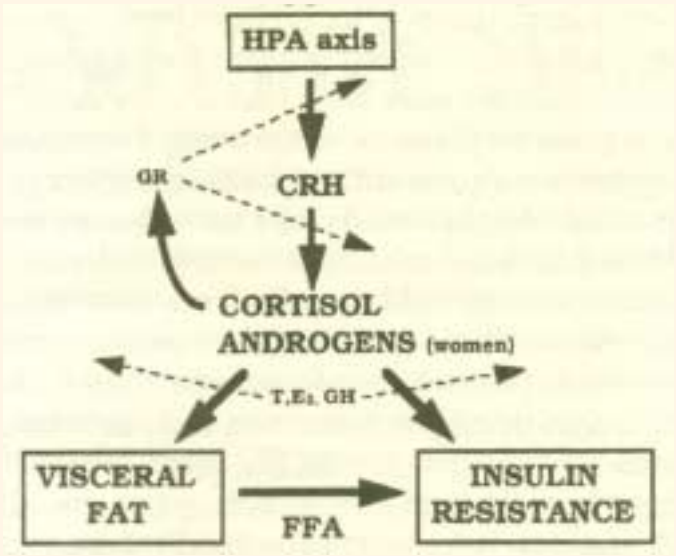
As estrogen levels fall, most women develop an increase in abdominal fat near the skin that you can pinch, which Peeke calls the "menopot". This is not nearly as dangerous as fat stored deep in the belly designed to protect abdominal organs. Heredity, hormones, eating and exercise habits can all influence this visceral fat but "toxic stress" is emerging as a key player. Peeke believes that **if we overeat when we are under stress, fat is preferentially deposited deep in the abdomen** so that the liver will have ready access to fuel that might be needed for future fight or flight responses. She has also shown that deep belly fat cells have the largest number of receptors for cortisol so that the hormone is attracted to this area.

While not everyone who is under stress overeats and the majority of obese persons do not have elevated cortisol levels there is growing support for the stress-visceral obesity-insulin resistance syndrome link. The major cause of this is hypersensitivity to and/or hyper-responsiveness of the HPA axis but other endocrine abnormalities have also been observed in association with visceral obesity. Increased HPA activity and cortisol inhibit the production of growth and gonadal hormones but there may be gender differences. Signs of masculinization in females with visceral obesity as well as Cushing's disease are likely due to HPA hyperactivity that stimulates adrenal secretion of androgens, as well as cortisol.

Obesity Is More Than Just Overeating

The multiple endocrine perturbations resulting from increased hypothalamic-pituitary-adrenal activity during chronic stress have peripheral consequences. Cortisol in the presence of insulin increases

the tendency to lipid accumulation. Since visceral fat has a much higher concentration of cortisol receptors than other fat depots, the greatest accumulation is in belly fat. These actions are normally opposed by sex steroids and growth hormone but levels of these are also suppressed during stress.



The above diagram is adapted from a 1993 article by Per Björntorp entitled **Visceral obesity: a 'civilization syndrome'.** As depicted, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis during stress results in a corresponding increase in cortisol secretion and inhibition of growth and gonadal hormones. Cortisol redistributes fat from other adipose tissue stores to visceral fat depots. Increased visceral obesity together with other endocrine changes resulting from chronic stress leads to insulin resistance that is further amplified by free fatty acids (FFA). The controlling effects of testosterone (T), estrogen (E_2) and growth hormone (GH) on both visceral fat accumulation and insulin sensitivity are diminished due to their inhibited secretions.

Other contributors to visceral fat include Cushing's syndrome, menopause and aging, excess alcohol intake, chronic depression or anxiety because these are all characterized by high cortisol and insulin and/or low sex steroid and growth hormone levels.

Stress also contributes to insulin resistance when increased secretion of adrenaline and noradrenaline result in the breakdown of glycogen stores that increase the demand for insulin. In addition, stress can contribute to obesity by influencing not only what and how much we eat but also when. In a prior Newsletter I related my experience at Walter Reed when I was able to show that obese Army officers would either gain or lose weight on the same 1000 calorie/day diet depending on when the calories were consumed.

Night Eating Syndrome (NES), in which over 50% of daily food intake is consumed after 8 PM, is characterized by decreased appetite during the day but an increase at night, a tendency to eat sugary or starchy foods, feeling tense, anxious or guilty while eating, insomnia and eating if you wake up at night. NES may occur in up to a quarter of obese individuals and appears to be related more to stress than hunger according to a recent study. Researchers showed that, compared to controls, NES patients had markedly different ACTH and cortisol responses following injection of corticotropin releasing hormone (CRH) which stimulates the body's response to stress.

It is generally assumed that if you are overweight it simply means that you are taking in more calories than you burn off - so the only solution is to eat less and increase your physical activity. Diet and exercise are obviously of prime importance but genetic, cultural, behavioral, metabolic and other factors may also play a role. A family history of obesity increases the chance of being overweight by 30 percent and while some of this results from familial eating and exercise habits there may also be a hereditary link if you have a mutated version of the leptin gene.

Dopamine deficiency has been linked to a variety of addictive behaviors and recent research suggests this may be true for some obesity patients. As we shall see, there is also mounting evidence that obesity can be due to a virus, which might explain the present epidemic and also lead to new treatment approaches.

Leptin, Dopamine, Ad-36, Ghrelin, Supplements And Other New Approaches

Why certain individuals are overweight or obese may involve much more than how many calories they consume or expend. We can all probably think of people who seem to be able to consume several thousand calories a day without putting on a pound while others continue to gain on 800 to 1000 calorie diets. The usual explanation is that their "metabolism" is different and since hyperthyroid patients tended to be thin despite increased food intake, thyroid was frequently given to help patients lose weight. Although patients with underactive thyroids and myxedema are puffy they are almost never overweight due to increased fat deposits. It is doubtful that more than 1 percent of excess weight problems are due to hormonal or metabolic disorders. More plausible players in the cast of characters that may contribute to new obesity therapies include:

Leptin - (from the Greek *leptos* meaning thin) is a protein produced by fat cells thought to suppress appetite. Genetically obese mice can't make leptin and lose weight dramatically when given leptin. While obese patients don't have leptin deficiency, large doses of leptin have been shown to promote weight loss in some but it may have more promise in helping prevent weight gain.

Dopamine - receptors for this pleasure-reward neurotransmitter have been found to be diminished in obese patients who may use eating as a way to bring on pleasure. Improving dopamine function may be much safer and more effective than appetite suppressant and fat blocking drugs.

Viral Infection - Can you catch obesity like you catch a cold? Might sound crazy but nobody ever dreamed that peptic ulcers and stomach cancer could be due to helicobacter infection. Adenovirus-36 (Ad-36) makes chickens and mice gain significant amounts of fat without any increased food intake. In one study of 52 obese patients, the 10 who showed evidence of Ad-36 infection were the ten most obese. A trial on antiviral agents and a vaccine to prevent the infection is in the wings.

Ghrelin - is called the "hunger hormone" because it rises significantly before meals and plummets afterwards. Although it is produced in the stomach, its receptors are in the brain where it stimulates growth hormone secretion. The name derives from the root *ghre*, which means growth in Hindi and ghrelin causes weight gain in laboratory animals by increasing food intake and decreasing its utilization. In human studies to investigate effects on growth hormone, 80 percent of subjects said ghrelin caused intense hunger and blocking it might reduce appetite and obesity.

Numerous nutritional supplements ranging from appetite suppressants and stimulants to various types of fiber or fat blockers as well as combinations of these are aggressively promoted as weight loss products. Very few can supply reputable studies to support their claims and some have been associated with serious side effects and deaths. We will discuss these and other products that have scientific support for efficacy and safety in a future Newsletter. We will also tackle the thorny subject of the best diet to reduce insulin resistance and obesity and the significance of the Glycemic Index; our next Congress will deal with all of these topics — so stay tuned!

Health and Stress
The Newsletter of
The American Institute of Stress
124 Park Avenue Yonkers, NY 10703

ANNUAL SUBSCRIPTION RATES:
E-MAIL..... $25.00
PRINT (DOMESTIC)..... $35.00
PRINT (FOREIGN)..... $45.00

ISSN # 1089-148X

Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief
www.stress.org
e-mail: stress124@optonline.net