Orentreich
Foundation for the
Advancement of
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HEALTH LONGEVITY LETTER

As this letter was being written, an article was published the day before Thanksgiving in the Journal of the American Medical Association. It reported that among 83,818 female nurses studied for 16 years those who ate 5 or more ounces of nuts per week reduced their risk of developing Type II Diabetes (DM2) by 27%; those women who only ate 1 to 4 ounces of nuts a week had a 16% lower incidence of DM2. It was not determined whether the intake of the nuts' unsaturated fats and/or their rich source of antioxidants and other nutrients were responsible. The women who ate nuts frequently also tended to weigh less than the others after the 16 year study.

Previous studies also have shown that including nuts such as walnuts and almonds in a normal-calorie diet 1 to 4 times per week decreased the risk of cardiovascular disease (CVD) by 27%. Risk was decreased by 50% in persons eating nuts more than 5 times a week.

Metabolic Syndrome X—we call it MSX in this letter—is at other times loosely referred to as Metabolic Syndrome, Syndrome X, Insulin Resistance Syndrome, Impaired Glucose Tolerance, or Hyperinsulinemia. Although MSX always includes insulin resistance, sometimes evident by a high fasting blood insulin level over 14 IU/L, insulin resistance can exist independently of MSX. MSX is a precursor of DM2 and a major risk factor for CVD. It effects 20% of the US population and is clinically associated with at least 3 of the following 5 criteria:

- abdominal obesity (circumference > 35" for women and > 40" for men at widest girth)
- high blood pressure (> 130/85mmHg)
- high fasting blood glucose (> 110mg/dl)
- high fasting blood triglycerides (> 150mg/dl)

low fasting blood high density lipoproteins (< 40mg/dl for men and 50mg/dl for women)

What is MSX?

MSX is a cluster of metabolic disorders that typically involves insulin resistance and obesity. Insulin resistance occurs when the body's cells do not respond to the normal amounts of insulin that the pancreas releases into the blood stream in response to dietary glucose. Insulin controls the level of glucose in the blood and plays an important part in regulating how cells use carbohydrates (sugars and starches), fats, and proteins to build and repair tissues. The pancreas compensates for insulin resistance by releasing more insulin. This excess insulin can cause tissue damage. But as insulin resistance increases, the extra insulin released by the pancreas might be inadequate to control blood glucose levels, and that is when DM2 and significant health problems begin in genetically predisposed individuals; these include impaired ability to heal, nerve damage, kidney failure, coronary artery disease, and loss of vision, and they only worsen with age.

Information for Donors
The Orentreich Foundation for the Advancement of Science, Inc. was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. It is duly registered with the United States Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

Your tax-deductible contribution should be mailed to:
Orentreich Foundation for the Advancement of Science, Inc.
910 Fifth Avenue
New York, NY 10021-4187

Genes, Nutrition, and Lifestyle
You can assess your genetic tendency to MSX with a careful family history. Although the genetic component cannot be altered, you can reduce your propensity through nutritional and lifestyle changes: reducing your weight (some say as little as 10%) by eliminating excess calories and increasing your physical activity.

Given that a high-carbohydrate, high-calorie diet with resultant weight gain can lead to MSX in some individuals, it is perhaps not surprising that the health risks associated with such a diet, particularly one high in fructose and sucrose, mimic those of MSX. (See page 4.)

The Glucose Insulin Tolerance Test
Beyond getting a thorough family history, you can further evaluate your current MSX status with the oral Glucose Insulin Tolerance Test (GITT).

The GITT evaluates your glucose-insulin interaction by measuring your ability to respond to the stress of a defined amount of glucose. The GITT is accomplished by fasting overnight, then drinking a highly sweetened beverage (the challenge) followed by hourly blood collections over three hours to monitor the changing levels of glucose *and* insulin in response to the challenge. The oral Glucose Tolerance Test follows the same procedure but measures only the level of glucose response; it is not as revealing as the GITT**.** An abnormal response in the levels of glucose and/or insulin to the challenge could be an early indicator of MSX. (Note: A normal fasting glucose level does not mean that response to a glucose challenge will also be normal.)

The Special Role of Fructose
While sucrose (ordinary table sugar) is half fructose and half glucose, it is fructose that holds the most interest because it binds more readily to the body's proteins than glucose making it more likely to produce detrimental substances called *Advanced Glycation Endproducts (AGEs). AGEs* are major contributors not only to cataracts but also to detrimental age-related changes in many body tissues, for example, artery wall stiffness and lax, sallow skin. For this and other reasons the American Diabetes Association very recently began advising diabetics to limit their intake of fructose, which had been a staple of diabetics' diets.

It has been hypothesized that the increase in the prevalence of insulin resistance and MSX in developed countries results from a near total reliance on processed foods coupled with sedentary living. While sucrose intake has increased significantly in the last century, fructose consumption has risen some 26% in the last 30 years, not only because it is part of sucrose but also because it is contained in *high fructose corn syrup*, which is both sweeter than sugar and requires smaller amounts to flavor foods and drinks. This ubiquitous sweetening agent is found in virtually all sweetened processed foods—everything from carbonated drinks to ketchup, fast foods, salad dressing, and even bread.

Although fructose is chemically similar to glucose, the body handles it very differently. Once absorbed by the small intestine, fructose neither raises the concentration of glucose in the blood nor stimulates secretion of insulin by the pancreas. These are the reasons that fructose (and sorbitol, which the body converts to fructose) have long been used as sweeteners in foods specially prepared for diabetics.

Published data, however, suggest that excess fructose is far from harmless. In fact, in some ways it might be worse than excess glucose, not only because it so readily forms *AGEs,* as mentioned above, but also because of the way it is metabolized. Within the cells of the liver, fructose bypasses certain of the metabolic controls on glucose metabolism and, although the liver can convert fructose to glucose, *fructose is more readily converted to fat* in the form of triglycerides. Controlled defined diets with human

subjects have found, for example, that substitution of fructose for even a fraction of dietary glucose can elevate blood levels of cholesterol and triglycerides as well as blood pressure.

Yet, in proper measure and timing, fructose is probably not a bad thing. In fact, recent nutritional studies with both diabetic and normal human subjects have demonstrated that small amounts of fructose taken 30 to 60 minutes before a meal actually act like insulin and help the body dispose of the glucose ingested during the subsequent meal (mostly eaten as starchy foods such as potatoes, bread, rice and pasta). Thus, the time-honored dietary tradition of a fresh fruit appetizer before a meal now finds scientific support.

Research at OFAS

In our ongoing effort to prevent age-related disease and extend healthy life expectancy, OFAS is actively investigating the impact of insulin resistance and MSX along with the benefits of restricting consumption of fructose and sucrose and the taking of medicinal supplements.

OFAS investigations include:

- ***developing a database of oral GITT test results***
- ***using the Serum Treasury to confirm that low DHEA/S levels in men are an indicator of sub-clinical insulin resistance***
- ***evaluating glycosylated hemoglobin blood levels as an index of AGE production***
- ***using hair samples (a non-invasive method) to assay the production of AGEs using the Serum Treasury to correlate breast, pancreatic, and prostate cancer with insulin resistance and MSX***

We believe that discovering how and why specific nutrients contribute to causation or prevention of age-related diseases will yield practical ways to prevent them, for example, the inclusion of nuts as noted above, and we envision a future where dietary modifications will play an important part in extending healthy life expectancy.

We look forward to sharing with you future developments from our research and that of others in the field.

All of us at OFAS thank you for steadfastly supporting us in our goal to develop interventions that prevent, halt, or reverse disorders that decrease the quality or length of life.

ABNORMAL BLOOD CHEMISTRIES	COMMONALITIES	
	METABOLIC SYNDROME X	HIGH FRUCTOSE AND SUCROSE DIET
High Cholesterol	ü	ü
High Triglycerides	ü	ü
High LDL (Low Density Lipoproteins)	ü	ü
High VLDL (Very Low Density Lipoproteins) Small, dense LDLs especially	ü	ü
Low HDL (High Density Lipoproteins)	ü	ü
Decreased Adiponectin (fat cell protein)	ü	Under investigation
High Uric Acid	ü	ü
Chronically Elevated C Reactive Protein (indicator of inflammation)	ü	Under investigation
High Glycosylated Hemoglobin	ü	ü
Increased Plasminogen Activator Inhibitor #1 (Increased Clotting)	ü	Under investigation
ABNORMAL GLUCOSE/INSULIN METABOLISM		
Insulin Resistance/Hyperinsulinemia	ü	ü
Impaired Glucose Tolerance	ü	ü
Diabetes Mellitus Type 2	ü	ü
Increased Activity of 11β-Hydroxysteroid Dehydrogenase (HSD) in Adipose Tissue of Obese Human Beings	ü	ü
CLINICAL SIGNS & CONSEQUENCES		
Intra-Abdominal (Central) Obesity	ü	ü
Hypertension	ü	ü
Gout	ü	ü
Kidney Failure	ü	ü
Heart Disease	ü	ü
Stroke	ü	ü

To avoid the potential damage of a diet high in fructose and sucrose, which is ½ fructose, limit intake of:

processed foods and beverages made with sugar, fructose, high fructose corn syrup, or sorbitol
concentrated sources such as dried fruits (raisins, apricots, prunes, apples)
excess honey
jams, jellies, and candies
syrups, such as maple, molasses, corn (containing high fructose corn syrup)
chocolates with added sugar
foods intensively browned by high temperature cooking, especially those with added sugar (creates AGEs)

Artificial sweeteners and foods prepared with them are fine if they do not also contain fructose, sucrose (which is ½ fructose, ½ glucose), and/or sorbitol (which the body converts to fructose).