May 2002 Issue | Walter Willett, MD

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Welcome to Functional Medicine Update for May 2002. This month our Ninth International Symposium on Functional Medicine takes place at the Diplomat Resort & Spa in Ft. Lauderdale, Florida. I hope you have signed up and will join us for this extraordinary meeting on brain biochemistry and neuropsychiatric and neurophysiological function. We are going to have a great time over the Memorial Day Weekend, May 25-28. I look forward to seeing you there.

This month in FMU we will focus principally on nutritional decisions—how they are made and how they influence functional health over the course of aging. We have as our Researcher of the Month, Walter Willett, MD, Chairman of the Harvard School of Public Health. With more than 500 publications to his credit, Dr. Willett has guided us all in our thinking.

In assessing the food/health relationship throughout the history of FMU, we have looked at associations; epidemiology, anthropology studies, animal data, cell culture work, and information, from a wide range of disciplines. We first created a hypothesis and then built what we hope is a testable methodology to evaluate nutritional relationships to health and disease

With the publication of a recent paper in the *New England Journal of Medicine,* we have occasion to consider once again which is better, drugs or foods, for the prevention of coronary disease. That article is titled "Simvastatin and Niacin, Antioxidant Vitamins, or the Combination for the Prevention of Coronary Disease."[1] Based on epidemiological data, many experts have predicted that each 1 percent reduction in the level of low-density lipoprotein (LDL) cholesterol results in a reduction of 1.0 to 1.5 percent in the risk of major cardiovascular events. They further predict that every 1 milligram-per-deciliter increase of high-density lipoprotein (HDL) brings about a 2 to 3 percent reduction in the risk of cardiac events. This relationship now appears to be independent of LDL levels, so the HDL/LDL ratio becomes important.

Comparing Simvastatin and Niacin to Antioxidants
To evaluate different methodologies for reducing cardiovascular disease incidence and progression of atherosclerosis, the authors of this paper used the statin drug simvastatin, along with slow-release niacin, given at twice-daily doses ranging from 250 mg to 1000 mg for four weeks. They contrasted that protocol with individuals who also received antioxidants or antioxidants plus niacin and simvastatin, versus a placebo. The antioxidant vitamins administered were 800 IU per day of *d*-alpha-tocopherol (vitamin E), 1000 mg of vitamin C, 25 mg of natural beta-carotene, and 100 mg of selenium. These formulations were compared to a placebo capsule given on a daily basis to patients with varying degrees of atherosclerosis. The participants' cholesterol level was monitored and plaque formation was evaluated by angiography. It was a detailed study that compared lipoprotein fractions and degree of stenosis.

Simvastatin plus niacin had a synergistic effect on many of the functional parameters related to cardiovascular function—lowered number of proximal lesions, reduced stenosis, and mean change in minimal luminal diameter. All of these parameters improved with the simvastatin and niacin therapy, which was much more effective than simvastatin alone. Antioxidant vitamin supplementation alone had a slight positive impact beyond that of placebo, but it was not statistically significant. A very wide range of variability, however, suggested inter-individual changes.

Personalized Nutrition
Matching the right nutrition program with the right individual, or personalized nutrition, is a theme of this month's *FMU* as it has been in previous issues. Therapeutic programs are not a one-size-fits-all situation. A general concept that antioxidants are good for everybody may not be true in this instance. A wide range of variability exists from person to person. The efficacy of antioxidants did not achieve statistical significance as did the simvastatin/niacin combination.

When antioxidants were added to the simvastatin/niacin in another arm of the trial, some parameters improved, but others did not. In no case, however, did they improve over the simvastatin/niacin program. In fact, the effects were less evident than with simvastatin and niacin. Simvastatin/niacin produced the best results; simvastatin plus antioxidants was not as good. You do not get positive synergy; you may get antagonism. Antioxidant vitamins by themselves did not reach the level of statistical significance. There is a drift toward improvement, but with signs of high inter-individual variability. They were not as good as either arm of the trial, but better than placebo.

Simvastatin plus Niacin: the Best Results
The authors of this study conclude that contrary to the hypothesis that antioxidants might provide the greatest benefit in early lesions, they had no effect on stenosis in the 0-29 percent of the luminal diameter group. The clinical and angiographically measurable benefits of simvastatin plus niacin were greater than would be expected from statins alone, suggesting that niacin lends another positive benefit beyond that of the HMG CoA reductase inhibition effects of statin drugs.

The combination antioxidants with simvastatin and niacin resulted in a big surprise. Arterial and clinical benefits tended to diminish in comparison with those achieved with simvastatin and niacin alone. The adverse interaction between these two therapeutic strategies reached the level of statistical significance of P=0.02. This interaction appears to result from substantial and specific effect of antioxidant vitamins on blunting the expected increase in the level of HDL2 that niacin stimulants. The effect applied to the roughly 40 percent of patients with coronary disease who have low HDL cholesterol levels but rarely use combination therapy targeted at both LDL and HDL.

Raising HDL
Several things can be employed to raise levels of beneficial HDL, including thyroid hormone T3, modest amounts of exercise, niacin, and chromium. Antioxidants do not appear to have a favorable effect in this regard. In fact, they may actually lower HDL.

The authors of this study conclude that antioxidants alone do not provide demonstrable statistically significant benefit over simvastatin and niacin therapy. There may be some individuals, subgroups, or cohorts, for whom antioxidants are very important, at least the vitamin E/beta carotene/vitamin C/selenium amounts used in this study. Others may actually exhibit adverse effects. Again, one size does

not fit all.

Vitamin E is more than just an antioxidant. It has an important intracellular communication role. A recent article in *Nutrition Reviews* discussed the way vitamin E may relate to cell signaling to influence atherogenesis.[2] It inhibits platelet aggregation and proinflammatory activity of monocytes. Therefore, it may lower the risk of smooth muscle proliferation and endothelial function. It may actually change the kind of plaque that is formed, causing plaque to be more plastic or fluid and less likely to dislodge, break off, and stimulate platelet adherence in a thrombus formation. The composition of plaque may change as a consequence of vitamin E, as might the dynamics of the arterial wall and the stickiness of white blood cells that undergo transmigration to become foam cells.

We cannot conclude that just because fewer small atherosclerotic lesions are present in the arterial wall, they necessarily exhibit reduced pathogenicity. Lesions may present with different levels of pathogenicity, and vitamin E may play a role in the reduction of pathogenicity as a consequence of its effect on monocyte-macrophage function, arterial wall adhesion, rolling and migration, and ultimately the production of oxidized LDL

Just as vitamin E is a modulator of intracellular communication in addition to being an antioxidant, the role of vitamin C also extends far beyond its antioxidant benefits. The authors of a recent paper in the Lancet talked about the preventive effects of vitamin C on carcinogenesis.[3] They point out that many dietary phenolic substances have stronger antioxidant effects than vitamin C when tested in vitro. However, the mechanism for the inhibitory actions of vitamin C on carcinogenesis may go beyond its antioxidant effects. These investigators noted that vitamin C has a preventive effect on inhibition of hydrogen peroxide-induced gap-junction intercellular communication.

Gap-Junction Intercellular Communication
In other words, like vitamin E, vitamin C plays a role in modulating certain types of intercellular communication. Gap-junction intercellular communication is essential for maintaining the homeostatic balance through modulation of cell proliferation and differentiation in the multicellular organism. Inhibition of gap-junction intercellular communication is strongly related to the carcinogenic process, especially to tumor promotion. Hydrogen peroxide, a known tumor promoter, induces inhibition of gap-junction intercellular communication and hyper-phosphorylation of connexin43 protein, a gene response element.

The investigators studied the effects of vitamin C on gap-junction intercellular communication and phosphorylation patterns within the connexin43 gene. They found vitamin C played an important role in buttressing against hydrogen peroxide and its effect on gap-junction intercellular communication, much more than other free radical scavengers such as propylgallate or trolox. Propylgallate and trolox are, in fact, far better antioxidants than vitamin C, but they are not nearly as effective as modulators of gap-junction intercellular communication.

Anti-Tumor Effects of Vitamin C
The investigators in this study pointed out that vitamin C might, therefore, have an anti-tumor-promoting effect through a mechanism other than its straight antioxidant mechanism. They suggest its mechanistic basis might be through its modification or inhibition of gap-junction intercellular communication initiated by such free radicals as hydrogen peroxide.

The bioflavonoid quercetin also plays an even more powerful role than vitamin C, on a mol basis, in modulating gap-junction intercellular communication. A combination of vitamin C and quercetin, therefore, may have favorable effects.

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Soy protein and soy isoflavones also have favorable effects on serum lipids. Postmenopausal women who consume 56 to 90 mg of isoflavones of soy protein daily can help normalize cholesterol and reduce their statistical risk of heart disease. One may ask if, at that level, there might be an adverse effect on thyroid function or estrogen receptor binding sites, or some other deleterious endocrine effect.

A recent paper in the American Journal of Clinical Nutrition looked at the effect of soy protein at the two levels I described, 56 or 90 mg per day as isoflavones, in postmenopausal women. The researchers found no adverse effect on any of the endocrine parameters they measured. Those parameters included FSH,

testosterone, estrogen, progesterone, estrogen metabolites including the 2- and 16-hydroxylated estrogens, thyroid, thyroid-stimulating hormone, and DHEAS.[5] None of these hormones was adversely influenced by the regular intake of soy at the above doses, which would be considered normal dietary intake of two to three portion sizes of soy products per day. This research comes from a noted group of collaborators from several centers who have finally helped us recognize that soy does not pose the risk some people propose in terms of endocrine dysfunction, including thyroid dysfunction.

Soy isoflavones also reduce oxidative stress in men and women and alter the oxidizability of serum lipids, including LDL. This may represent another beneficial effect on the dynamics of soy isoflavones, other than their cholesterol-modulating effects. They may also influence the immunological parameters related to inflammation and atherosclerosis. The authors of a recent paper in Cancer Letters discuss the effect of soy isoflavone supplementation on these markers of oxidative stress.

Several years ago, Dr. Kilmer McCully brought to our attention another atherosclerosis risk factor that can be modified by diet. It is the condition related to folic acid (B12) and homocysteine. Dr. McCully is a former FMU Clinician of the Month. Recent research has revealed that 30 percent plus of the US population carries a unique genetic susceptibility called the methylenetetrahydrofolate reductase polymorphism (MTHFR). These individuals can be homozygous or heterozygous. Homozygous cases represent 10 to 12 percent of the population, or about one out of 8 or 10 individuals. These individuals cannot process dietary folate effectively into the active methylating form of folate called 5-methyltetrahydrofolate.

A recent paper in the American Journal of Clinical Nutrition describes individuals with the MTHFR, 677C→T polymorphism, or single nucleotide polymorphism (SNP) and discusses their response to either folic acid or 5-methyltetrahydrofolic acid supplementation.[7]Individuals with the homozygous recessive form of this condition respond favorably to 5-methyltetrahydrofolate, which means they can lower their homocysteine and achieve appropriate production of the methylating agent, S-adenosylmethionine (SAM). That is the active methylating agent the enzyme catechol-O-methyltransferase uses to transfer methyl groups to neurotransmitters and bioamines to phospholipids, and even to detoxify hormones to create appropriate function.

A beneficial nutrition program for individuals who carry the MTHFR polymorphism might include either increased levels of folic acid (preferably by supplementation, a more absorbable form than food folates, which are polyglutamyl folates) and/or 5-methyltetrahydrofolate as a specific supplement to bypass the metabolic susceptibility found in their genotype. This metabolic susceptibility is what we might call the "small wire," the MTHFR polymorphism

Individuals with increased serum lipids, particularly triglycerides and the dense LDL particles, may be exhibiting the metabolic syndrome Dr. Gerry Reaven, in a past FMU Clinician of the Month interview, described as syndrome X. A recent paper in the Journal of the American Medical Association discusses the effects of diet and simvastatin on serum lipids, insulin, and antioxidant levels in hypercholesterolemic men.[8] This was a randomized, controlled trial. The investigators used a modified Mediterranean diet rich in omega 3 fatty acids. This diet potentiated the cholesterol-lowering effects of simvastatin and counteracted the fasting insulin-elevating adverse side effects of the statin drug. (Simvastatin increases insulin resistance and fasting insulin levels.) Unlike simvastatin, the diet also did not result in decreased

levels of either beta-carotene or coenzyme Q10.

A dietary intervention program along with a statin drug improved physiological endpoints and reduced risk, a synergistic effect. We often talk about choosing between diet and drugs, but this appears to be an instance in which they are compatible and can be used in combination for synergistic improvement.

The metabolic syndrome called syndrome X is not uncommon in our society. Depending on the degree of severity, it can be seen in as many as 20 percent of the population. These are individuals who may be on their way to becoming type-2 diabetics or to experiencing cardiovascular events even before those disorders can be diagnosed.

A recent paper in the Journal of the American Medical Association suggested that unadjusted and age-adjusted prevalence of metabolic syndrome were 21.8 percent and 23.7 percent, respectively, in the United States. Certain ethnic groups have an even higher prevalence, up to 42 percent in Native Americans. Pima Indians, for example, have a significantly increased metabolic risk based on various susceptibility factors, diet, and lifestyle.[9]

Extrapolated to 2000 census data, this remarkable information suggests that about 47 million Americans have metabolic syndrome. It may be one of the most important precursors to later-stage disorders, including type-2 diabetes.

Metformin or Lifestyle Intervention in Diabetes Management
A paper in the New England Journal of Medicine is titled, "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin."[10] This study compared the efficacy of metformin, which is the most common drug used to manage type 2 diabetes, to that of lifestyle intervention with diet and exercise. The authors discussed the important role nutrition will play in the future of medicine as we learn more about how to individualize programs and improve compliance with better products and more "patient-friendly" programs.

This trial compared diabetes prevention with medicine to prevention with diet and lifestyle changes. It found both lifestyle changes and treatment with metformin reduced the incidence of diabetes in people at high risk, but lifestyle intervention, diet, and exercise were more effective than metformin

This metabolic syndrome interrelates not only with the relative risk of heart disease, but also with other endocri

ne abnormalities. One such abnormality is menstrual irregularities in women as a consequence of insulin's interaction with 17, 20-lyase in the ovaries. This enzyme is responsible for the production of androgens. Hyperinsulinemia and insulin resistance are associated with polycystic ovary syndrome (PCOS) and hyperandrogenicity. In fact, hyperandrogenicity is the most common endocrine dysfunction found in menstruating women. It is much more common than hypoestrogenism. Symptoms of hyperandrogenicity include facial hair, acne, changes in body composition, increase in visceral adipose tissue deposition, menstrual irregularities, and eventually ovarian cysts.

PCOS is the late-stage diagnosis from an earlier stage increasing severity of insulin resistance that interferes with menstrual cycling and ovulation. That was the subject of a paper in the Journal of the

American Medical Association. Investigators found long or highly irregular menstrual cycles were a marker for risk of type 2 diabetes. This risk resulted as a consequence of increasing severity of insulin resistance, hyperandrogenicity, altered hormonal balance between estrogen and androgens, and the resulting reproductive and menstrual irregularities in these young women.[11] If the symptoms remained unrecognized, the condition could later worsen and develop into diabetes.

Interacting Variables in Etiology of Endocrine Disorders
We can begin to put these things together as a web of interacting variables. In fact, according to the authors of the above-cited article, one third or more of diabetes mellitus cases are undiagnosed in the general population. Although screening bias (i.e., greater sensitivity of screening for diabetes in women with irregular cycles) might contribute to observed results, these authors consider it an unlikely explanation for the fact that women with the menstrual irregularities (altered cycles, menorrhagia) later are much more likely to develop diabetes. An examination of their insulin levels often reveals that these women are hyperinsulinemic and insulin-resistant.

When we view these endocrine disorders from a functional perspective, we can see that diet and lifestyle may be more important as primary therapies than early intervention with medications

Some investigators have studied insulin mimetics that actually improve insulin sensitivity and lower body weight, suggesting that body fat deposition may come as a consequence of a metabolic irregularity. It was not fat that caused diabetes. It was a metabolic disturbance that led to the dysregulation of insulin, leptin, neuropeptide Y, and the array of neuroendocrine hormones. This hormone disruption, in turn, leads to the repartitioning of calories into storage form, to adipocyte accumulation of fat in preference to the use of fat to produce mechanical or cellular energy.

This is the topic of a recent paper in Nature Medicine. In animal studies, the authors discuss insulin mimetics and how they can lead to weight loss without even putting an animal on a calorie restriction diet, because of their influence on the cellular economy, this neuroendocrinology of weight control.[12]

Diabetic Dyslipidemia and Insulin Resistance
Elevated triglycerides and reduced HDL levels in patients are associated with metabolic syndrome and insulin resistance. Circulating triglycerides and free fatty acids are common features of the diabetic dyslipidemia and are associated with insulin resistance, according to an article in a recent issue of Nature Medicine.[13] This condition is also associated with the genetic production of elements like the protein resistin, which leads ultimately to central obesity and in a later stage correlates with type 2 diabetes.[14]

Leptin replacement therapy has been found useful for lipodystrophy, the increasing lipid deposition in central adipose tissue. This condition is interrelated with insulin signaling and with other hormones of the hypothalamus/pituitary/adrenal, hypothalamus/pituitary/thyroid (HPA, HPT) axis.[15] It is also interrelated with stress, diet, environment, and exercise patterns. It signals the glucose transporters, telling them how to transport glucose and regulate cellular energy economy at the mitochondria. This information represents a new perspective on the role of nutrition in the function of the organism. It represents a new chapter in the field of functional medicine

INTERVIEW TRANSCRIPT

Walter Willett, MD

Chairman
Harvard School of Public Health

JB: We have a distinguished guest as our Researcher of the Month. Walter Willett, MD, is a professor of medicine at Harvard Medical School. He took his postdoctoral training in medicine and in public health at Harvard. He is chairman of the Harvard Medical School Department of Nutrition and has published more than 500 articles on epidemiology and the evaluation of eating habits and their relationship to chronic degenerative diseases. Dr. Willett is a major contributor to our understanding of the role of nutrition in medicine and disease.

Dr. Willett, it's a privilege to have you as our Researcher of the Month. What led you from your background in medicine into the field of nutrition?

WW: I was interested in nutrition from the beginning. I was a vegetable grower putting myself through college. I studied food science in college at Michigan State University before going on to medical school. It's been a theme all the way through my work. Back in the 1970s, when I was looking at dietary recommendations, people were being given very strong messages about what to eat and what not to eat. When I scratched the surface to see where the evidence was to support those recommendations, I realized there wasn't much there.

The recommendations were based on hypotheses and best guesses, but the evidence was very limited at that time. For example, people were told that eggs were one of the worst possible things you could eat and something you absolutely had to avoid if you wanted to reduce your risk of heart attacks. You would have thought there had been studies showing that people who ate more eggs had higher risk to heart attack. In fact, there were no such studies.

The Need for Prospective Nutrition Studies
It seemed to me that it was necessary to develop large prospective studies where we could collect data on what people were eating. We needed to follow them over decades of time to see what happened to them and then relate the specific aspects of diet to the ultimate risks of heart disease, cancer, and various outcomes. That led to setting up the dietary component of the Nurses' Health Study and the Health Professionals Followup Study that followed from that.

It has been an illuminating experience. We found that many of the hypotheses we had in the beginning have not held up with the real tests of data. Many of the things that have turned out to be important are aspects of diet that we did not consider important at all back in the 1970s.

Research Highlights
JB: When you reflect on your discoveries, what are some of the important things you have learned from evaluating 250,000 men and women epidemiologically over the years?

WW: The primary hypothesis we began with in our first funded study, which started in 1980, was that fat intake was the major reason for high rates of breast cancer in Western countries. We have repeatedly analyzed that data over time and have found no evidence that women who have higher fat intake are at

high risk to breast cancer. In fact, the association is even slightly in the opposite direction. We are trying to understand that a little bit better right at this time.

The whole area of fat as the major evil factor in the diet was very dominant back in the early 1980s when we began, and conversely, because fat was bad, people were told to eat very large amounts of starch and carbohydrate. As the data have come in, we have not seen any evidence for anything showing total fat in the diet is an important factor in the etiology of that disease.

Importance of Type of Fat in Diet

What has turned out to be very important is something that was suspected a long time ago, even in the 1960s and early 1970s. It is that the type of fat is important. Back then people were told to replace saturated fat with polyunsaturated fat. That has proven to have a good impact and probably explains much of the decline in coronary heart disease in the United States and other western countries.

We've added to the complexity about fat type by learning about trans fat. In the 1970s the vast majority of us, even nutritionists, were unfamiliar with trans fat. Now we know it is by far the worst type of fat in terms of the epidemiologic evidence relating diet to risk of cardiovascular disease. Metabolic studies have now shown conclusively that trans fat, on a gram-for-gram basis, is far worse than saturated fat and accounts for what appears to be a large part of cardiovascular disease. That is one of the major findings in the study.

Importance of Carbohydrate Type and Glycemic Index

We have also seen that the total amount of carbohydrate in the diet is not so important, but the form of carbohydrate does turn out to be important. This idea, partly represented by the concept of glycemic index, has been at the fringes of nutrition for a number of years. Dr. Jenkins in Toronto developed that concept. We have seen that the glycemic index does play a major role in causing diabetes and cardiovascular disease. The glycemic index represents large amounts of rapidly absorbed carbohydrate in the diet. That leads to increased insulin responses and seems to exacerbate the insulin resistance syndrome. We see it showing up as high risk of type 2 diabetes and, as I mentioned, risk to coronary heart disease.

One interesting aspect of the glycemic index or glycemic load that also takes into account the amount of carbohydrate, is what we describe as an interaction between an underlying degree of insulin resistance and the glycemic load of the diet. In a very small study, using only 10 women, Dr. Gerry Reaven in California found the women who had higher insulin resistance had a worse response to high carbohydrate intake. They had higher triglycerides, lower HDL, and higher insulin levels than the leaner women, or women with lower insulin resistance.

We have also seen that in our large epidemiologic studies. Women with above-average body weight are more insulin resistant and have a worse risk with higher glycemic load in the diet than thinner women. That explains, in part, why traditional Asian populations—Chinese, Japanese—could eat high carbohydrate diets and not have high cardiovascular disease rates. That is almost certainly because their insulin resistance was very low due to their being very lean and physically active. But in more Western lifestyles, now including the urban areas of those Asian countries, those same kinds of diets are not tolerated so well and we see skyrocketing rates of diabetes.

Eat, Drink, and Be Healthy

JB: I want to mention your book so our listeners can follow up with some additional reading and studies. It is Eat, Drink and Be Healthy.29 I found it one of the great overviews in this field. The Table of Contents includes such topics as Healthy Weight, Surprising News About Fat, Carbohydrates for Better and Worse, Choosing Healthier Sources of Protein, The Fruits and Vegetables Story, You Are What You Drink, Calcium, Take a Multivitamin for Insurance, and Recipes and Menus. It is a good follow-up source for our listeners.

Fat Type and Prostate Cancer Risk

I'd like to continue with the dietary fat proposition. In a paper that appeared in the Journal of the National Cancer Institute a number of years ago, you studied beef fat and prostate cancer in males.30 One of the fatty acids you teased out of your regression analysis that appeared to be associated with prostate risk was a-linolenic acid, the omega 3 unsaturated fatty acid. That seemed to be counter-intuitive to a lot of individuals who found that ALA tended to prevent prostate cancer in animal models. Would you help us understand that?

WW: It was a bit of a surprise to see that pop out of the data. We, too, had seen a-linolenic acid as being beneficial for coronary heart disease, and it does seem that a lot of people are not getting enough a-linolenic acid in their diet. As we pointed out in that paper, when we probed further, it seemed this was probably really not a-linolenic acid. When we looked at the sources, it was only a-linolenic acid from beef that was causing problems, not from vegetable sources, which is where most of us get linolenic acid. For example, we get linolenic acid in salad dressings, where the soybean oil is not partially hydrogenated, or from canola oil. We saw no excess risk associated with those sources.

There seemed, ironically, to be sort of a marker for beef fat intake and something about red meat or beef fat was associated with prostate cancer risk. It probably wasn't really a-linolenic itself, since it didn't seem to be consistently associated. It was coming from other sources. That's one of the reasons why, when we do these kinds of analyses, just taking simple numbers out of the computer is dangerous. You really have to look at the foods where it is originating and see if the data are internally consistent that way.

Dietary Fat/Carbohydrate/Protein Ratio

JB: One area of controversy for many docs right now has to do with the ratio among fats, carbohydrate, and protein calorie percent. Your studies point us more toward the composition of the individual macronutrients, in contrast to looking for a specific ratio. A lot of publicity has been given to specific ratios of fat to protein to carbohydrate, and less attention has been paid to the composition of each of those components. What is your opinion about that, based on your work?

WW: That's a clear read of what I've tried to convey in the book. That's what the data have shown very clearly, not just in our own research, but in metabolic studies as well. Again, the type of fat in the diet seems to be much more important, with trans fats being something we should eliminate if at all possible from our diets if we want to be maximally healthy. We should also keep saturated fat low, although obviously every diet will contain some saturated fat. Monounsaturated and polyunsaturated fats are actually beneficial. They lower LDL blood cholesterol levels and reduce risk of heart disease. Many people are getting into serious trouble and increasing their risk to heart disease because they've tried to eliminate a number of the essential polyunsaturated fats from the diet, both a-linolenic acid and other omega 6 fatty acids.

What we were just talking about applies to carbohydrates as well. The type of carbohydrate seems more important than the amount. Large amounts of highly refined starch and sugars in the diet are deleterious. They are just empty calories. We've known that for a long time. Now we're seeing that they really do exacerbate the insulin resistance syndrome, which is linked to so many major diseases. That's a core problem in nutrition and well being in this and other Western countries.

A Flexible Ratio

There is probably quite a bit of flexibility with the actual percentages of calories from fat or carbohydrate, as long as they're healthy fats and carbohydrates. On average, though, I think the metabolic studies support a higher percentage of calories from fat than some people advocate. I think you can also have a healthy diet with higher carbohydrates and lower fats if you are very careful about the form of those carbohydrates in the diet.

The same applies to protein. There is probably a fair range of healthy percentage of calories from protein in the diet. What the different forms of protein are is probably not as important as what comes along with that protein. Obviously, the problem when you eat beefsteak to get your protein is that you also get a lot of other things that are not so healthy. If you eat more nuts, legumes, chicken, and fish as protein sources, they come with a better mix of fatty acids and other micronutrients.

Importance of Fruits and Vegetables

JB: We all know that eating five or more fruits and vegetables a day or more would be wonderful. What is it in those fruits and vegetables that imparts a unique health-promoting benefit? There's been some controversy about whether you can take out one nutrient at a time, like vitamin E from soy, or b-carotene from a carotenoid-rich vegetable, and administer it as a solo nutrient to get the same effect that you would get with a complex mixture. How do you view this field of antioxidants and the complex mixture of redox-active substances in foods?

WW: Each individual fruit or vegetable is an incredibly complex mixture of compounds, and each one is different from the others in terms of the balance of those mixes. A few years ago the idea was circulating that fruits and vegetables had an almost magical ability to reduce cancer risk dramatically.

The data from the larger prospective studies that have come in over the last two or three years point to a much weaker association between fruit and vegetable consumption and risk of cancer than we had thought before. Most of the studies up to that time had been case-control studies, in which dietary information is collected after the diagnosis. That's just a setup for bias in recall and reporting of dietary information. There is still some benefit, but eating a lot of fruits and vegetables is certainly not a substitute for not smoking or staying lean and exercising, in terms of cancer prevention.

Folic Acid

In terms of specific compounds in fruits and vegetables with regard to cancer, the one for which there is increasingly strong evidence of benefit is folic aid. We now have definitive proof that getting enough folic acid can dramatically reduce risk of neural tube birth defects. That has had a big impact. We could have made a very general statement that there is something about the diet of lower-income individuals that is making them generally unhealthy. We could have said that if they were to eat more fruits and vegetables we were pretty confident the risk of neural tube defects would go down. But it's valuable to know that a specific, purifiable chemical, folic acid, is responsible for that reduction in neural tube

defects.

That understanding can allow much more focus on intervention, by fortification or supplementation. We know it's really hard to get whole populations to shift their fruit and vegetable intake, even slightly. In my lifetime, we could never get enough of a shift to get everybody up to 400 mg of folic acid per day.

Foods or Food Constituents
In some instances, some definable constituents of foods can be responsible for powerful beneficial, or perhaps negative, health effects. It is also possible that there are some aspects of whole foods that are interactive, so complex, and composed of such multiple constituents that we may not be able to simulate them very well in a supplement. I think we should keep an open mind about this and pursue all possibilities.

I'm pretty pragmatic about it. If we can identify a specific compound and it's most effective to choose that in supplementation and fortification, I think we should take advantage of that knowledge. But sometimes our information just isn't well enough developed to know what it is about a fruit or food that is effective. Therefore, it's still pragmatic to indicate or encourage greater consumption of those whole foods.

Moving from Gross Deficiency Indicators to Subtle Biochemical Indicators
JB: Many years ago I interviewed Dr. Smithells about anencephaly and spina bifida prevention with periconceptual folate and B12 supplementation. In 1982 he published in the Lancet a case-control study on supplementation that was not well received by his colleagues. At that time, the dominant theme was that spina bifida, the most prevalent birth defect in the Western world, had little if anything to do with nutritional status, especially because it did not produce a frank deficiency, such as megaloblastic anemia, microcytic anemia, or some other aberration.

We have come a long way, moving from gross morphological indicators of deficiency to more subtle physiological or biochemical indicators of insufficiency. It is particularly significant in people at risk, such as those with the MTHFR polymorphisms, in whom there may be an increased genotype of risk.

WW: That's absolutely right. When Dr. Smithells showed folic acid has an incredibly important health impact, even without signs of clinical deficiency, he created a turning point in nutrition. When I was in medical school, I was taught there was no benefit in additional vitamin intake beyond the elimination of the signs and symptoms of clinical deficiency. That concept was demolished by the folic acid/neural tube defect research.

Epidemiologic studies are now showing additional adverse effects of low folic acid intake, including increased risk of colon cancer, breast cancer, coronary heart disease, and probably stroke. Those aren't as definitively proven as the neural tube defect, but the evidence is pretty strong for all of those benefits of higher folic acid intake.

Neural Tube Defects as the Tip of the Iceberg of Folic Acid Importance
In some ways, neural tube defects are much easier to study than the chronic diseases that develop over decades. We know within about a two-week window when the critical period is in terms of prenatal exposure to folic acid. We know you have to follow women for nine months, and then you find out whether there is a neural tube defect or not. You don't have to follow people for 25 or 30 years to find out

what happens to them. It looks like the folic acid and neural tube defect story was just the tip of the iceberg, but really of monumental importance as a turning point in nutrition.

Single Nutrient Tests: The Finnish Smokers Study

JB: Several years ago researchers in Finland conducted a study to determine if b-carotene supplementation was effective in protecting smokers against lung cancer. In this often-cited Finnish Smokers Study, b-carotene supplementation actually seemed to produce a negative effect in some individuals. Earlier animal studies had shown that monkeys supplemented with carotene and forced to drink alcohol sustained damaging effects. Their livers converted carotenoids into retinoids that might have affected cell differentiation and influenced mitogenesis. Perhaps the Finnish Smokers Study shouldn’t have been unexpected, since the subjects were alcohol consumers and cigarette smokers, and b-carotene was the only nutrient studied. How do you view the design of some of the experiments to test a hypothesis?

WW: It's almost a sociological phenomenon. The evidence that b-carotene might be beneficial for preventing lung cancer was pretty weak at the time the study started. The Physicians' Health Study was the first study, and it had already been designed as a randomized control trial of aspirin or placebo for preventing coronary heart disease. As long as they were following people, it seemed easy and inexpensive to add the b-carotene component to that study. But then many people decided they needed to have a b-carotene study, and they started more than 30 randomized trials. It probably would have been better just to let that one play out, since the evidence wasn't so strong. At the end of the Physicians' Health Study, the results showed neither harm nor benefit from b-carotene.

Interestingly, we now have data that we didn't have at the time those studies began, looking prospectively at b-carotene intake from fruits and vegetables. We don't have any epidemiologic studies of people taking b-carotene supplements, but we now have prospective epidemiologic evidence looking at b-carotene intake and lung cancer risk. We do not see any relationship between intake, even from fruits and vegetables, and lung cancer risk, after we controlled very carefully for cigarette smoking. The Finnish Smokers Study was premature. If we'd had that kind of epidemiologic evidence, no one would have tried to do a b-carotene trial. It was a pretty long shot when it started.

The Peto Study

JB: Did that trial derive out of the proposition of Doll and Peto? I recall an article in which they challenged the community.

WW: That was Richard Peto's study. They published a provocative and interesting paper in Nature that was very influential.31 They looked at a number of case-control retrospective studies that suggested people who ate more fruits and vegetables had lower rates of lung cancer. It was a long-stretch hypothesis without any direct epidemiologic support, that b-carotene might be the responsible factor. It was a creative, interesting hypothesis, but again, b-carotene was one of hundreds of compounds in fruits and vegetables that might have been protective.

We have to be creative. We need hypotheses, and many of them will be rejected, but there were probably too many eggs in the basket of one hypothesis. If anything, that is probably what we can learn from this in retrospect.

Vitamin A and Postmenopausal Hip Fracture

JB: You were a principal author of a recent paper in JAMA on the subject of vitamin A intake and hip fractures among postmenopausal women.32 This is moving from provitamin A to retinol itself. The results you got are interesting to a variety of people who may be supplementing daily with vitamin A-containing supplements. Would you tell us what the implications might be?

WW: This was a bit of a surprise to us. Basically, we did this analysis because some colleagues in Sweden were trying to understand why people who drink more milk did not have a reduction in fractures. That's what the prospective epidemiology studies show. Despite the milk-moustache campaign, the epidemiologic evidence is pretty consistent showing no substantial benefit for high dairy product consumption and fracture risk.

Our Swedish investigators were trying to look at this in more detail. They were looking at some of the things in milk. One is vitamin A, because milk is often fortified with this vitamin. What they found was an increased risk of hip fractures with higher vitamin A intake. This is preformed vitamin A intake, the kind that's in supplements or the kind that's in liver, not the kind in fruits and vegetables.

Increased Hip Fractures with Increased Retinol Intake

That was one finding that obviously needed to be reproduced, so we looked at this in the Nurses' Health Study, where we had about 18 years of followup of women we were monitoring for fracture risk. We did confirm that finding fairly strongly from a statistical standpoint. It was quite a robust finding. We saw increased risk of hip fractures with higher intake of retinol, the preformed vitamin A. Interestingly, this increased risk started to take off just about at the current U.S. RDA level. That is worrisome, because a lot of people are getting much more than that. If you take a multiple vitamin, typically have fortified breakfast cereal, drink fortified milk, and maybe get a little it from some other foods, a large part of the population is consuming more than the current U.S. RDA.

The practical implication of this is that multiple vitamins are good because they ensure that we get enough folic acid. But we should probably be looking for multivitamins that contain less than the 5000 U.S. RDA amount of vitamin A, or in which part is in the form of b-carotene. I certainly think people should not take specific vitamin A supplements unless it is medically prescribed for a specific indication. For example, in retinitis pigmentosa, there is evidence of benefit for taking vitamin A, but that should be done under medically supervised conditions, perhaps with some bone density monitoring. Given that this is seen now in several studies and there is good biological basis for this, avoiding high intakes of preformed vitamin A is probably a good thing.

Differences in Types of Vitamin A

JB: Some of our listeners may be unfamiliar with the difference between provitamin A or carotenoids like b-carotene and preformed vitamin A. Would you explain how the body controls the production of retinol from carotenoids? There may be those who fear they might have a problems if they eat a lot of dark red-orange vegetables.

WW: It is important to be clear that there's no problem with eating lots of fruits and vegetables, including carrots, which contain a lot of potential vitamin A. That vitamin A is in the form of carotenoids, mostly b-carotene. We have an enzyme that cleaves b-carotene right down the middle and breaks it into two molecules of retinol. Retinol is the more biologically active form of vitamin A. In recent years we have

found that we actually control that cleavage process. It is a regulated process, and if we don't need vitamin A, we don't keep as much b-carotene. It's a protection.

Interestingly, if you think about it, natural human diets contain very little preformed vitamin A. The only substantial source of preformed vitamin A is liver. We put a lot of preformed vitamin A into our diets with fortification and supplementation, way beyond what people would normally be eating. It looks like we've probably gone a bit too far in that direction. It has helped to prevent vitamin A deficiencies, but it looks like we need to reduce some of those fortification and supplementation doses.

The Importance of Nutrition

JB: I'd like to close with a question that is a bit more philosophical. A physician seeing patients has a number of concerns and a very limited amount of time to spend with each patient in which to make a diagnosis and develop a treatment program. Nutrition may not seem important to that doctor in the range of concerns. How important is nutrition, really? Why are we making such a big deal out of it?

WW: I can add to that issue. Until very recently, the evidence wasn't strong enough to give clear, well-founded nutritional advice in many areas. But as the data have come in, it does appear that nutrition, coupled with other aspects of a healthy lifestyle such as not smoking and regular activity, has profound effects.

We published a paper in the New England Journal of Medicine about a year and a half ago (Meir Stampfer was the first author), in which we looked at how much heart disease could be prevented with good diet, not smoking, and physical activity.33 We found that more than 82 percent of coronary heart disease could be prevented by moderate, easily obtainable kinds of nutrition and lifestyle changes. We've done a similar analysis for stroke and found more than 70 percent can be prevented; for type 2 diabetes it is over 90 percent; for colon cancer it is over 70 percent. The potential impacts of nutrition are huge. They are much more significant than using statins or other kinds of pharmacologic interventions. If we want to have a big impact on health, it has to be achieved through nutrition.

Recognizing the Difficulty of Making Dietary Changes

Having sat opposite patients for years as well, I understand these changes don't come easily. Sometimes it seems we aren't accomplishing very much, and we often don't have time to educate patients adequately.

In fact, that's one of the reasons I put together this book, Eat, Drink and Be Healthy, because I think it's something physicians can give to patients and they can invest a couple of hours reading it. It’s a pretty small investment when your health is at stake. It can help convey some of the knowledge and some of the background, but it's still the physician's message that really indicates how important this is for everyone's health.

Spreading the Word on Nutrition

JB: That's a wonderful admonition, support, and encouragement for those who are listening. I hope we can spread this information. Your book, Eat, Drink and Be Healthy, is a great place to start in this discovery and to help educate patients. Thanks so much for being with us, Dr. Willett. Keep up the tremendous work.

WW: Thank you. It's a real pleasure to be your guest. It's a great way to get information out there.

n the development of personalized nutritional approaches, I want to focus on Dr. Johanna Lampe's work. A research professor at the Fred Hutchinson Cancer Research Center in Seattle, she has a remarkable publication record, and her research exploration has been very productive.

Dr. Lampe examined the effects of fruits and vegetables, assessing mechanisms of action by which various phytonutrients might play a role in improving health. In a paper that appeared in the American Journal of Clinical Nutrition, she describes various ways phytochemicals could help modify function.[34] In Table 2 in this reference, she examines antioxidant activity, modulation of detoxification enzymes, immune system stimulation, alteration of cholesterol metabolism, blood pressure reduction; antibacterial and antiviral activity, and a number of potential positive relationships between various phytochemicals found in specific foods and functional outcomes in humans.

Benefits of Garlic and Other Vegetables

In another article, Dr. Lampe discusses garlic (Allium sativum) and garlic concentrate and the potentially dramatic effects of some of the active sulfhydryl compounds in garlic on the binding by pathogenic bacteria like Helicobacter pylori to the GI mucosal surfaces.[35] In this paper, which appeared in Nutrition and Cancer, Dr. Lampe and her colleagues showed that a concentrate of garlic inhibited the growth of Helicobacter pylori, an etiologic agent for peptic ulcer disease as shown by Dr. Barry Marshall, in bacteriological media.

In a paper published in the Journal of the American Dietetics Association, Dr. Lampe looked at vegetables, fruits, and legumes and their effect on urinary excretion of both lignans and phytoestrogens, the isoflavones we often associate with soy.[36]

In another study, she examined the relationship of urinary isoflavones and lignan excretion patterns to the intake of soy, vegetables, and fruit. This paper, which appeared in Cancer Epidemiology, Biomarkers & Prevention, looked at statistical relationships of food intake, asking what individuals eat these fruits and vegetables and how well they absorb some of these phytochemicals.[37] Are they excreted, and how are they processed? How are they metabolized in the body? Dr. Lampe and her colleagues were trying to understand who might respond and who might not respond to different types of nutritional intake, in terms of personalized nutrition.

Soy Isoflavones and Equol

Dr. Lampe found that some women who consume soy isoflavones excrete a metabolite called equol, and other women do not.[38] Equol excretion seems to have a unique relationship to a woman's secondary metabolic function. According to Dr. Lampe and her colleagues, the women who excrete equol after consuming soy may have a different type of bacterial flora, and the gut flora may play a role in processing some of the soy isoflavones and delivering different products to the body.

When they examined consumption of wheat bran and soy protein and their relationship to urinary excretion of equol in premenopausal women, Dr. Lampe again found a wide variation from woman to woman in the amount of equol excreted based on how much isoflavone they took in. Some women, who seemed to be non-excreters, basically made no equol. Others, called equol excreters, had varying degrees of excretion. The ratio of excreters to non-excreters was about 50/50, among women who were studied and discussed in this paper, which appeared in the Journal of Nutrition.[39] The authors suggest that equol

secretion depends on relationships among the GI milieu, the GI flora, food, the digestive process, and ultimately a hormonal messaging system or altered intracellular communication.

Fiber and GI Bacteria
In looking at gender differences in colonic function in a randomized trial, Dr. Lampe and her colleagues evaluated different types of fibers and their relationship to types of gut bacteria. They found significant gender differences in GI responses when mean and women were given identical intakes of dietary fiber in various . This paper appeared in the journal Gut.[40]The observed differences, presumably, were a result of different bacterial flora, tying together the whole discussion about the GI signaling system, the immune system of the gut, the GALT (where 50 percent or more of the immune system is clustered), and communication with gut contents and bacterial flora.

This leads us to a consideration not only of soy, but also of a variety of foods known to be metabolized by certain bacteria into secondary metabolites, including the lignans from flax and other foods.[41] We know these substances are also hormonal modulators. Bacterial flora in gut metabolism modify not only modify the metabolism of isoflavones but of lignans as well. The gut is an important part of the story of secondary metabolism of these biomarkers.

Drug Interactions with Newer Antidepressants: The Role of Cytochrome P450s

How does this relate to the genetics of detoxification? We know about drug interactions with various medications like the cytochrome P450 2D6 polymorphisms and individuals who are slow metabolizers of SSRI drugs and may have a higher risk to adverse effects of SSRIs. These same genetic polymorphisms that metabolize drugs in different ways also metabolize different nutrients and phytochemicals in different ways, including bioactive ingredients from herbal products like silymarin, St. John's Wort, or echinacea. A recent paper in the Journal of Clinical Psychiatry describes drug interactions with polymorphisms of the detox enzyme system, the cytochrome P450s.[42]

Phytochemicals found in a variety of foods modify the function of the detox enzyme systems. For instance, the glucosinolate-containing cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, cabbage) will modify the detox enzyme expressions of the cytochrome P450 and, to some extent, the phase II enzyme systems. Ingesting various types of vegetables may produce different effects on your detox enzyme systems. This situation is discussed in a paper that appeared in Nutrition and Cancer.[43] These authors looked at the fact that even if you steam vegetables, if you have the proper GI system, you can still digest and release these secondary metabolites like indole-3-carbinol that modify gene expression and detox systems.

Glucuronidation Polymorphisms and Detoxification
Dr. Lampe has now completed a series of studies showing nutrition impacts detoxification in a number of ways through glucuronidation and other secondary metabolic pathways through the cytochrome P450s. A paper titled "Prevalence of Polymorphisms in the Human UDP-Glucuronosyltransferase 2B Family: UGT2B4($D^{458}E$), UGT2B7($H^{268}Y$), and UGT2B15(D85Y)1" shows the glucuronidation process varies from person to person.[44]Similar variations were observed in the UGT1A family of glucuronosyl transferases.[45]

A paper that appeared in Cancer Epidemiology, Biomarkers & Prevention discussed the modulation of human glutathione S-transferase by differing dietary intake.[46] This paper, also by Dr. Lampe, describes the differences among allium vegetables, cruciferous vegetables, or brassica-type vegetables in altering glutathione transferase expression of differing types, GST-α, GST-μ and GST-τ. Of particular interest were the GSTM1 and GSTT1 null polymorphisms. Different genotypes yield different responses.

A more recent paper compares the effects of different types of vegetables on cytochrome P450s and phase II detoxification and the influence on caffeine clearance as a model for liver detoxification.[47] Once again, different individuals have different responses. In general, however, the crucifers had an effect that was effect from that of the apiaceous vegetables or allium vegetables. You can imagine personalized diets based on the phytochemicals in individual food families linked up with a person's own genotype to express the phenotype of best expression of function, compression of morbidity, and extension of the individual's health span.

Using Epidemiological Information to Individualize Programs
Dr. Willett described his work on epidemiology looking at statistical evaluation of general effects in the population, and using that information to individualize intakes in people. Treatment can be personalized, because one person's healthy food may be poisonous for another. We are constantly trying to find how to get the maximum benefit for the individual. This is the future of functional medicine in the age of genomics and proteomics. It will be a continued theme as we design diets specifically for individuals and their own polymorphisms.

Thanks for being with us. We will visit again in our June issue.

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