March 2007 Issue | Jorn Dyerberg, MD Medical and Scientific Advisor

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Welcome to March 2007 *Functional Medicine Update*. Have you ever stood at a corner knowing that when the light turns and you cross the street you are going to have an experience on the other side that you didn't expect? That is how I feel as we head into this issue of *FunctionalMedicine Update*. I feel we are standing-all of us-on the corner of a paradigm shift in medicine.

This month's clinician/researcher of the month, Dr. Jorn Dyerberg, is one of the two discoverers of the fish oil concept. You will hear how he and his colleague, Dr. Bang, came to the remarkable discovery that fats in the diet of Greenland Eskimos were associated with a lowered risk of disease (which was totally alien and contrary to any opinion at that time because it was felt that all fat was dangerous to the vascular system). That discovery in the 1960s is typical of the mounting evidence before us as we stand on this corner waiting for the paradigm shift in medicine to occur.

I will go through this information with you and describe just the tip of the iceberg of what has been changing over the last month or two in the field of health care-things that you see, feel, hear about, and are experiencing in your own practices. You will recognize that we are all standing on a street corner, waiting for the light to change. And when we do walk, we are going in a different direction than we've been taking in medicine over the past 50 years.

Let's start this month with a recent editorial that appeared in the *New EnglandJournal of Medicine* in 2006 that was titled "Dangerous Deception-Hiding the Evidence of Adverse Drug Effects." [1] This is by Jerry Avorn from Harvard, who has written very eloquently about the field of drug safety and has done quite a bit of work-in fact, he is the author of a best-selling book on this topic. This editorial demonstrates why we are at a corner waiting for the light to change. I quote, "September 30 is becoming a day of infamy for drug safety." It was on September 30, 2004 that Merck announced that rofecoxib (Vioxx) doubled the risk of myocardial infarction and stroke. The company withdrew the drug from the market after 5 years of use and more than 20 million patients, representing more than 3 billion dollars in annual sales. This action was a consequence of reports by a number of investigators.

Adverse Reactions Recently Linked to Aprotinin

In a similar, more recent situation, Mangano et al. found that patients who were given various drugs ended up with very serious difficulties. [2] The Mangano et al. study was looking not at Vioxx, but rather at aprotinin, which was approved in 1993. Further evaluation of this drug showed that patients undergoing uncomplicated coronary artery surgery who were given aprotinin had a

55{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} increase in the incidence of myocardial infarction or heart failure, and a 181{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} increase in the incidence of stroke or encephalopathy. One has to wonder how a drug could be approved that would later show dramatic adverse side effects.

Another editorial appeared in *The NewEngland Journal of Medicine* in 2006 titled "Observational Studies of Drug Safety-Aprotinin and the Absence of Transparency." [3] This editorial, authored by William Hiatt, goes on to talk about how we could miss-based upon the mechanisms of evaluation for drug safety-a potential series of side effects from aprotinin when used in clinical practice, a drug that was used routinely in the operating rooms of all hospitals that were doing the CABG (Coronary Artery Bypass Surgery). On the date of September 30, 2004, when Merck announced the recall of Vioxx, it further strengthened concerns about the way in which drug safety is determined.

The recall of Vioxx opened up questions about the major classes of medications (both prescription and over-the-counter) that are used commonly for the management of many chronic-related health problems. At the head of this list are medications used to treat inflammation, which we now recognize represent the underlying etiology for so many of the chronic, age-related diseases. And then we might start looking at things like cardiovascular outcomes with diclofenac, or even something simple, like ibuprofen.

Long-term NSAID Use and Cardiovascular Disease
A study was reported in *The Lancet* in 2006 that looked at cardiovascular outcomes in patients with osteoarthritis and rheumatoid arthritis taking nonsteroidal anti-inflammatory drugs (this was the Multinational Arthritis Long-term Programme [MEDAL]). [4] What the investigators found was that there were not only increasing incidences of upper gastrointestinal clinical events (i.e. gastric hemorrhaging and bleeding), but also increased incidence of cardiovascular disease in individuals who were taking (over a long period of time) these nonspecific cyclo-oxygenase-inhibiting drugs. This suggests a general effect, with the impact seen most significantly on those drugs that have the highest efficacy, like rofecoxib. Rofecoxib was a marvelous drug for what it was designed to do: manage acute inflammatory pain for a very short period of time in people who have elevated, upregulated, inducible COX-2 activities. Unfortunately, these medications got extended into long-term chronic management of garden-variety pain and inflammation. This started producing (in susceptible individuals) the outcome predicted by Fitzgerald and others, which was the blocking of constitutive COX-2 activities in the vascular endothelium and lowering prostacylin (PGI2) production, inducing increased thromboxane and lowering the platelet anti-adhesive effects of prostacyclin, leading to clotting (with stroke) and heart attack.

There is an ever-growing story of cyclo-oxygenase inhibition that is not so pretty. It is not just gastrointestinal risk that leads to 12,000-15,000 deaths a year from acute bleeding, but it is also the chronic effects on the vascular endothelium blocking prostanoids (a constituent of cyclo-oxygenase derivatives) that can induce relative risks that were never seen before. It is no wonder that a paper appeared in the *Journal of the American MedicalAssociation* in 1997 that suggested that the 4 th-6 th leading cause of death in America is adverse drug reactions (to appropriate medications given to patients in hospital situations by well-trained professionals).

We had missed this over the many years because if you don't ask the questions you don't find the answer. It was assumed that people in hospitals often died, so we didn't look for the possibility that death was

amplified, or aggravated, or accelerated by medications given and the results these medications had on a person's unique biochemistry, or physiology, or genetics to produce an adverse outcome as serious as death.

This ever-growing story about things that could produce adverse effects over the long term includes chronic drug use. I'm quoting now from an editorial that appeared in *The Lancet* in 2006 called "The Ever Growing Story of Cyclo-oxygenase Inhibition." [5] Have we taken into account the risk-benefit trade-off on long-term management of chronic disease with new-to-nature molecules? Possibly there is a different kind of approach required if you are going to have a patient on therapy for months, years, or maybe even decades than that which you would use for a patient under short-term therapy in the emergency room or with an acute situation, or for whom the therapy is administered, the condition resolves, and the therapy is taken away.

FDA Recommends NSAIDS Carry Warning Labels about Long-term Use

Even those conditions that are associated with the use of over-the-counter anti-inflammatories are now being questioned as potentially of some concern. You have probably seen recently that the Food and Drug Administration (FDA) has proposed sterner warning labels for acetaminophen, aspirin, and ibuprofen, again cautioning Americans who take these non-prescriptive, nonsteroidal anti-inflammatory pain relievers of potentially serious side effects. Although they say that they remain safe and effective when used as directed (meaning short-term use), the Food and Drug Administration has said overdoses or long-term use can cause serious liver damage or even death. With aspirin, ibuprofen, or NSAIDs there is a risk of not only GI bleeding and kidney injury, but also increasing concern about cardiovascular disease risk.

So what I am really saying is that this is not insignificant. In fact, with acetaminophen, there is an estimated 56,000 people who go to the emergency room each year, making it the most common drug adverse side effect that produces acute symptoms, and these are not people who intentionally overdose. Many of these people are taking the doses that are recommended on the label, but they have unique biochemistry in the way they metabolize the compound, or they are poorly nourished, or they are drinking alcohol, which aggravates metabolism, producing toxic metabolites like NAPQI, which is the metabolite that has to be conjugated with glutathione in the liver. If glutathione is not adequately available, it becomes a hepatotoxic intermediate. We are starting to see dramatic changes in our thinking about the risk-benefit, or the safety relationships, of the use of pharmaceuticals over long term.

What do we do? People are growing older and do have chronic health problems, and we would like to think there is some remediation available. In an article in *Medical Hypotheses* in 2006, Dr. H.R. Hellstrom says it is likely that the risk of cardiovascular events and gastrointestinal adverse effects from COX-2 inhibitors (or COX inhibitors) can be reduced significantly by lifestyle preventative measurements. [6] Maybe there are things that we can do to improve our diet and our lifestyle that would make our bodies more tolerant to these medications, or maybe greatly reduce (or remove entirely) the need for them.

Often in life, as we are standing at the crosswalk waiting for the signal to say "Walk," we might wonder if some driver who is not paying attention to the red light will come rushing through the crosswalk. So before we step off-even before the sign says, "Walk"-we probably look both ways. By similar token, as it relates to where medicine is going, before we step off onto the walkway that represents the corridor down the pharmaceutical pathway, we might want to look both ways and ask, "Is there something coming?" If

so, we might want to stay on that corner or travel in the other direction.

It is this question that we are going to be talking about because certainly this story is not just related to cardiovascular or anti-inflammatory drugs; it has a spreading message. We saw disillusionment in the minds of millions of women when the Women's Health Initiative data on mixed conjugated equine estrogens and progestins was published, demonstrating that not only did these compounds not reduce the risk of heart disease (as had been told to women for many years), but they may have increased the incidence in specific women of heart disease, increased the incidence of cognitive decline, and had adverse effects upon immune system function. This disillusionment was extraordinary and led to (starting in early 2000) a reduction in the number of women taking hormone replacement therapy using equine estrogens and progestins. At the end of 2006, we saw-as maybe a fortuitous association, but maybe also a cause and effect-a dramatic report that for the first time in more than 15 years, data now indicates that the incidence of new cases of breast cancer are declining. [7]

Now this may be fortuitous and just one of those random associations with women ceasing to use hormone replacement therapy with equine estrogens and progestins. Or there may be something very significant that we should pay attention to about medicalizing and pharmaceuticalizing a natural process called menopause, and that possibly there are other ways that we would want to cross the street using a different crosswalk that would utilize other substances that are less potentially adverse, mitogenic, and cell-replicative-more traditional substances that have been used and sold to women for managing hot flushes and night sweats.

Statin Use is Becoming Pandemic

A more recent part of this story has to do with our excitement-almost an infatuation-for statins and the lowering of LDL cholesterol. We have seen this statin concept become so pandemic that it is almost required that a mid-life individual be on statins for promoting good health and longevity. In fact, it has been suggested that even youth possibly be administered statins prophylactically to lower cholesterol and purportedly reduce the incidence of cardiovascular disease as these children grow older. There has also been a recognition that if we could lower LDL while raising the favorable HDL cholesterol, we might have the best of all worlds (to decrease LDL cholesterol to 70 milligrams per deciliter or lower and increase HDL cholesterol above 50 would be a tremendously positive outcome).

Torcetrapib: Optimism Turns to Disillusionment

People have been looking for pro-HDL drugs that will activate the HDL-synthesizing machinery of the body. There was extraordinary excitement around a new drug that would, in fact, increase HDL cholesterol levels. It activated cholesteryl ester transfer protein (CETP). When I say "activated" what I really mean is that it reduced its function (the CETP), which then increased the effect on the body to regulate HDL (it increased the HDL form of cholesterol). This particular molecule, Torcetrapib, was eventually approved as a drug sold by Pfizer as a way of working with statins (Atorvastatin or Lipitor) to lower LDL while increasing HDL.

Not too long ago, we saw investor news in the pharmaceutical industry hailing and regaling the excitement about Torcetrapib, which was being promoted as an amazing new contribution to cardiovascular risk reduction and an amazing new profit generator for Pfizer. I'm now quoting from a press release in *Investor Weekly* that appeared just a little over a year ago, encouraging people to be very excited about this new drug and the combination of Atorvastatin and Torcetrapib.[8] Use and sale of these

products was expected to increase (and obviously increase profit for the company selling it), and it was presented as a good investor opportunity. So the CEPT inhibitor, Torcetrapib, and an LDL-reduction statin, Atorvastatin, looked like a wonderful recipe.

As we moved into 2007, that extraordinary optimism has been dashed on the rocks of disillusionment. Even though there was 800 million dollars invested into Torcetrapib, evidence adverse effects in some individuals has been found, and the drug has now been withdrawn from the market due to safety. Why didn't an FDA ethics committee intervene and why didn't we know about this? Certainly something went wrong.

Two senior Pfizer people said that trial results showed 82 patients taking Torcetrapib had died over the life of the trial versus 51 who were taking Lipitor alone. Torcetrapib was supposed to be combined with Lipitor and sold as a combination drug, but it doesn't look like it is ever going to make it to the market and be the success it had been proposed to be.

Did this result in-or at least contribute to-the recent news (in 2007) that job cuts are ahead for Pfizer? They are going to be domestically cutting their workforce down by 20,000 employees. They are going to be closing 5 plants and different research laboratories and production systems. This is a complex issue not just related to Torcetrapib alone, but related to pressure from generics, things coming off patent, and lack of an effective pipeline. [9], [10]

What I am really suggesting to you is that as we stand on the street corner waiting for the crosswalk light to come on, the world of medications is changing under us. In fact, one might say that Torcetrapib is really just kind of a case study of the change that is occurring within the field of pharmaceuticals. "Big Pharma," with its blockbuster medicines, is at a watershed that it has never really experienced before because of adverse side effects popping up in long-term surveillance trials.

Are We Entering the Age of the "Minibuster?"

It is very expensive to get drugs into the pipeline; the medicolegal system has put tremendous emphasis on improving safety profiles. We recognize from pharmacogenomics that people are different from one another and it cannot be expected that everyone will respond to a drugs the same way (as we used to think). It is more than just body surface area; it is related to cytochrome P450 and conjugation effects on how drugs are detoxified and how receptors are activated that results in tremendous genetic variation. We can't just wipe away adverse drug responses as being atypical and unexpected; they are (in certain genotypes) expected and reproducible. We may be moving from the age of the blockbuster to the age of the "minibuster"-drugs that are more targeted to specific genotypes, or limited away from those people who have adverse risk genotypes, like certain polymorphisms (the cytochrome P450s).

This changes prescribing patterns. This changes marketing. This changes sales. This makes it much more complicated to deliver a product that everybody embraces and it is good for all. This is the start of a new day of therapeutics in medicine. As the "Walk" light comes on and we start crossing the street-having looked both ways-we might find that the landscape on the other side has already changed by the time we get there.

With this as a backdrop, let's look at recent concerns in health care (like the epidemic increase in dysinsulinism, diabetes, heart disease relative risk, and other problems that occur from the inflammatory

conditions of altered insulin signaling). We recognize we are facing a global crisis for which we don't have (at present) a good solution that comes out of pharmaceutical science. It's as if we need a different model. It's as if the old model (molecules from the bench of lab chemists) is not necessarily well-suited to the management of long-term chronic problems. The pharmacopoeia that has been developed, which is very powerful for use in the emergency room or the critical care unit, may be a strategy for developing new molecules or medicines that is counter to long-term safety and good outcome.

What we have attempted to do is manage chronic disease (which constitutes 78{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of our healthcare expenditures) with drugs that were designed for short-term use for the management of acute problems without knowing what the long-term safety effects are when use of those drugs extends to decades of living. The first real test population for the effects of long-term use is the people who take them. Without any science upon which we can base the safety and effectiveness of drugs over the long term, the construct is starting to be recognized that maybe we are not really practicing scientific medicine when we extend use of short-term, high-potency drugs used effectively for crisis management into long-term patient care. This is a belief system not founded in real science; it is founded on the belief (or faith) that these drugs are going to be effective and safe, only to learn later that these products (many times) have shown to have less than acceptable safety or even efficacy profiles.

There is more and more evidence that indicates diabetes is becoming a worldwide epidemic of the 21 st century. This is discussed beautifully in a recent editorial that appeared in *The Lancet* in 2006 in which it is shown that the global burden of ischemic heart disease and stroke (beyond that of just type 2 diabetes) is much higher than we recognized in terms of burden of disease globally. [11] In addition to 959,000 deaths annually that were directly assigned to diabetes, there are 1,490,000 deaths from ischemic heart disease and 709,000 deaths from stroke attributable to elevated blood sugar, accounting for 21{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} and 13{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of all deaths from these conditions. It's like seeing the emperor with no clothes, finally, by shining light on him and he's not that attractive; this is a serious problem. The data I just cited is from an article titled "Global and Regional Mortality from Ischaemic Heart Disease and Stroke Attributable to High-than-optimal Blood Glucose Concentration: Comparable Risk Assessment." This appeared in *The Lancet* in 2006. [12]

What do you do? What are the drugs? What are the therapies? How do we stem the tide? Before we walk across the street, where do we want to put our feet? A very provocative study was recently published that I think helps us with some path finding in this area. The Finnish Diabetes Prevention Study looked at sustained reduction in the incidence of type 2 diabetes. [13] There wasn't a drug or a specific pharmaceutical used in this particular intervention. What was used was lifestyle intervention with diet, exercise, and counseling.

Sustained Lifestyle Changes Can Result in a Reduction of Diabetes Incidence

In this particular study, 172 middle-aged men and 350 women with impaired glucose tolerance were randomly assigned to either an intensive lifestyle intervention or control group. After a median of 4 years of active intervention, patients who were still free of diabetes were further followed for a median of three years (with a total, then, of about 7 years). Diabetes incidence, body weight, physical activity, and dietary intake of fat, saturated fat, and fiber were measured. The bottom line is that there was a statistically

significant reduction in type 2 diabetes in the individuals who complied with lifestyle intervention as their primary mode of therapy. In fact, per 100-person-years, there was a statistically significant reduction in type 2 diabetes in the P < .0001 level, indicating a 43{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in relative risk (or almost approaching half reduction risk over those people that didn't engage). There is presently no drug therapy that will accomplish that outcome. Lifestyle intervention (the authors concluded), in people at high risk for type 2 diabetes, resulted in sustained lifestyle changes and a reduction of diabetes incidence, which remained after the individual lifestyle counseling was stopped for the duration of the 7 years of the study.

Trial Involving a Thiazolidinedione Drug

Let's look at drug studies as contrasted to lifestyle studies for the management of these chronic illnesses (when I say "lifestyle" I am talking about diet, exercise, and stress management-types of programs). In a recent issue of the *Journal of the American Medical Association* in 2006, a study was published in which investigators (in a randomized, double-blind, placebo-controlled, multicenter trial) were looking at patients with type 2 diabetes and how their carotid artery wall was thickening over the course of intervention with a thiazolidinedione drug, pioglitazone. [14]

This particular study (conducted over 18 months) showed that pioglitazone slowed progression of coronary intima-mediated thickness (CIMT) compared with using a first-generation diabetes drug, which was a sulfonylurea. The study authors came to the conclusion that there maybe an advantage to using a thiozolidinedione or a peroxisome proliferators-activated receptor (PPAR) agonist over using a traditional sulfanylurea because the progression is slowed down.

How Does Lifestyle Intervention Compare to Metformin Use?

How does this compare to the implementation of a Mediterranean Diet, exercise, and stress reduction? What is the relative outcome in cardiovascular disease comparing the two? There was a paper published in *The New England Journal of Medicine* several years ago comparing metformin against lifestyle intervention in patients with type 2 diabetes.[15] This paper showed that both improved function, but that lifestyle, diet, exercise, stress reduction was superior to metformin.

The more we do these comparative studies, looking at how we modulate function-drug versus diet and lifestyle-the more we may become convinced that the best therapies are things that seem so simple, but are maybe unattractive because they don't sound exciting. It is easier to get something out of a bottle and take a pill a day than it is to have to do something by altering cellular signaling and cellular messaging by practicing good health.

In a recent issue of *The New England Journal of Medicine*, the question of whether thiazolidinediones are really the initial treatment of choice for type 2 diabetics is discussed (given some of the evidence that is emerging). [16] The author of the piece says that there does appear to be some emerging evidence of value, but there are also some adverse effects (like weight gain) that occur with thiazolidinedione drugs. The relative cost of these medications-their profiles of adverse events and their potential risk and benefits-need to be considered very closely before using them as the first line of therapy. It is suggested that with the modest glycemic benefit weighed against the risk of fluid retention and weight gain and higher cost, possibly we ought to stay with our traditional drugs like metformin for initiating pharmacotherapy for

type 2 diabetes.

The author does not talk about the fact that maybe both of these are not the primary therapies of choice. Maybe what we should be looking at are molecules that signal appropriate functional changes to the body, which are also the molecules that have come through the most significant and long-term laboratory study ever done-natural selection. These are molecules that have been associated with foods that historically have been associated with a low incidence of chronic, age-related diseases. Maybe we are looking in the wrong place for the molecules of choice.

There is an analogy you might have heard of about a man who has lost his car keys. He is bent under a street lamp at night trying to find them. Another man comes over to help him and says, "Can I help you look?" And the first guys says, "Oh yeah, but don't look here because I think I lost them over there where it is dark." So the second man asks him, "Well, why are you looking under the street lamp, then?" He says, "Well, it's the only place I can see." I think that analogy relates to some of the things we are doing in medicine right now. So before we step across the street when the "Walk" light comes on, let's make sure that we are traveling to the right side-that it is really the direction that we want to head.

In cases of very severe insulin resistance and metabolic syndrome associated with nonalcoholic steatohepatitis, you have fatty liver infiltration with an elevated liver enzyme profile. We are now seeing this in medicine for the first time with any prevalence. I can't remember 30 years ago (when I first started in this field) ever really seeing people who had nonalcoholic steatohepatitis. However now it is very frequent (even in younger people) to have these marginal liver enzyme elevations as a consequence of lipotoxicity from the infiltration of fat into the liver associated with insulin resistance.

There was a recent paper in *The New England Journal of Medicine* addressing the question of whether pioglitazone (one of the thiazolidinedione PPAR-gamma agonist drugs) is really the medication of choice for the management of, nonalcoholic steatohepatitis (NASH), the more acute form of metabolic syndrome.[17] In patients who had elevated liver enzymes and were administered pioglitazone, it did lead to metabolic and histologic improvement. However, in the editorial that follows (again weighing risk/benefit), the author, Arthur McCullough, goes on to say this evidence is promising, but not ready (yet) for prime time because of the potential risk of using these drugs over many years for chronic management.[18]

We recognize that these age-related increases in circulating inflammatory markers and altered insulin signaling really occur well before the onset of obesity, or elevated blood pressure, or elevated blood lipid. I think this is an important observation because we often think that these conditions are all caused by obesity and we wait until the patient is obese before we intervene with drugs. Now there is ever-increasing evidence to suggest that the early trajectories of these dysfunctions are associated with increased inflammatory markers: C-reactive protein, interleukin-6, interleukin-18, secretory intercellular adhesion molecule 1 (ICAM-1). All of these increase in the blood well before one starts to see increasing body mass index, increasing blood pressure with vascular endothelial resistance, and elevated blood lipid concentrations. Possibly, the effects are the outcome that we call obesity and the causes are things that have occurred within the subtle cell signaling processes of the body. These processes ultimately regulate function associated with heart disease, diabetes, and stroke that we see as changes in body composition like obesity, diabetes, heart disease (dyslipidemia), and, in fact, even in arthritis management.

Introduction of TNF Agents Increases Concern about Malignancy

You probably have seen there is some evidence now that autoimmune antibody-blocking agents (like the TNF-alpha blocking agents) may have some adverse effects in individuals when used for an extended period of time. In a recent article that appeared the *Journal of Arthritis Research and Therapy* in 2006, the authors say that the introduction of anti-tumor necrosis factor (TNF) agents and their now wide-spread use has resulted in increasing concern about malignancy and suppression of the immune system with opportunistic infection, including things like tuberculosis.[19] In addition, a recent meta-analysis of randomized clinical trials raised concerns about an increased rate of malignancy and infection in RA patients who were treated with these anti-tumor necrosis factor monoclonal antibodies.

Again, it is risk/benefit trade-off we are talking about. Are there different approaches that we might use to modulate these effects? The different approaches often come out of functional medicine and we have been talking about them for more than 25 years on this series. For instance, we now recognize that oral supplementation with things like *Lactobacillus acidophilus* (a probiotic which was not considered in the mainstream of medicine) can modulate intestinal pain in chronic irritable bowel syndrome because it alters opioid and cannabinoid receptor activities through modification of cellular signaling. These friendly bacteria set up a relationship with the gut mucosal receptors that sends up signals that downregulate the message of alarm that we then see as pain and as cramping.

How many drug targets are there? We are starting to recognize that the pharmaceutical industry is looking for ways of modifying cellular signaling because it is this signaling that ultimately controls (downstream) the production of tissue pathology. In an interesting paper that recently appeared in *Nature Reviews* in 2006, the authors talk about the fact that the pharmaceutical industry is now recognizing they need to find ways of modifying upstream events by modifying cell signaling, and they probably need multiple activities that are working simultaneously.[20] More than one molecule; mixtures of molecules. This is a whole different approach in pharmaceutical science than we have historically seen, which has traditionally been one molecule for one outcome.

When we look at how cell signaling influences chronic disease, we see emerging from *The New England Journal of Medicine* in 2006, a report that the asthma epidemic is associated with triggering events in gene response that produce multiple signaling outcomes that we see as inflammation.[21] Another article states that the new therapies for asthma will be things that modulate cellular signaling. I am now quoting from *Trends in Molecular Medicine* (a recent article by Peter Barnes that talks about the modification of these signaling pathways that are called kinases).[22]

Kinase Modulators will be New Therapeutic Agents

Similarly with neurodegenerative diseases, understanding the molecular causes of Parkinson's disease leads us back to understanding adverse cellular signaling of inflammatory nature, with oxidative stress and neuronal injury, and that the new therapeutic agents will be kinase modulators that are specific to the brain signaling process and reducing the inflammatory signals. [23] And even in the case of things like menopause symptoms and the risk to breast cancer, endometrial cancer, bone loss, and cardiovascular disease in women. I'm now quoting from a recent article in *Newsweek* magazine (January 18, 2007 issue) titled "Understanding Menopause." [24] These authors talk about using a lifestyle intervention diet to modulate hormone signaling. Such a diet would include the brassinoid vegetables-the cruciferous vegetables that contain glucosinolates that modulate hormonal metabolism, cell receptivity, and hormone

signaling. There was an interesting article in a recent issue of Science magazine that discussed how brassinosteroid signaling can modulate hormonal metabolism and effects at cell surfaces. [25]

We are seeing a transition in medicine occurring right before our eyes. There is really no better way to understand this than to hear the fatty acid story that we are going to learn about from our clinician/researcher of the month, Dr. Jorn Dyerberg. Dr. Dyerberg is a professor of medicine. He is one of the two pioneers in omega-3 fatty acid research who, in the 1960s and 70s, visited remote Eskimo settlements in Greenland and showed that the reason the low occurrence of ischemic heart disease was seen in these populations was due to the consumption of diets that were very high in omega-3 fatty acids from seals and fish. What we will learn from Dr. Dyerbeg is how this observation really frames a whole different paradigm in pharmacology and medicine that takes us away from new-to-nature molecules from the benches of synthetic chemists to those molecules in nature that might really modulate function, reducing the risk and incidence, and maybe even source of chronic, age-related diseases.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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We are here today with Dr. Jorn Dyerberg, a professor of medicine from Denmark who has done an extraordinary volume of work related to essential fatty acids and health, particularly focusing on cardiovascular disease. For those of you who may be unfamiliar with this, the story goes back more that four decades with Dr. Dyerberg and his colleague, Dr. Bang. I think this discovery will ultimately prove to be one of the great "a-ha's" that has occurred within the fields of nutrition and medicine and will save many millions of people from having unnecessary cardiovascular disease and a host of other chronic ailments. The question really is: Where did the concept come from?

Dr. Dyerberg, from your experience, obviously a good idea ultimately rolls forward to become a change in thinking. How did this all start for you?

Pioneering Work in Greenland
JD: It started way back-as you just said-nearly 40 years ago (in the 1960s) when I was a resident in Dr. Bang's department at a city hospital in Denmark. In our medical journal, there was a lead article pointing at our Danish citizens in Greenland, the Eskimos (because Greenland was a part of Denmark), stressing that in spite or their dietary habits (meaning, coming from the sea, from seals and whales with a high amount of fat), in spite of this diet high in fat, they had an extraordinarily low incidence of coronary heart disease. How come? The lead article said it was an obligation for the Danish medical society to go into that question before it was too late (meaning, before Westernized civilization, accompanied by high incidence of coronary heart disease, took over up there in the remote areas of Greenland). And Dr. Bang and I were fascinated by that story and said we would go up there and try to (if we could) elucidate that problem.

For me, as a young doctor, it was, of course, an opportunity for going deep into some esoteric aspects of

medical science, but also an opportunity to go and see these remote areas of the world and meet people, and that could be a fascinating experience. We arranged for our first expedition, which was in 1970. It wasn't that easy to get the money for that because not very many people supported nutritional science and not very many believed that there could be something to gain out of going up and seeing what diseases this tiny tribe of people had. But we managed to collect, I guess, $85,000, and that covered our expenditures for two months up there and we collected blood from the Eskimos.

We found out that they had a favorable lipid profile, but not to an extent that could explain why the number of heart attacks was as low as it was. So, we got sort of an explanation, but not the explanation we had expected. We were (rather strange enough) able to also analyze the fatty acid content of their blood. We had 130 samples of blood from Eskimos who were fasting. Dr. Bang said, "These are the only samples in the world. We have to do everything on them." And then we did fatty acids. And up came two fatty acids we had never heard about-two peaks on our chromatogram. And we said, "What are these?" I actually had to go to America-to Minneapolis to the Hormel Institute-to visit Dr. Ralph Holman, who was the expert (at that time, he has retired now) in identifying strange fatty acids. And he knew about some omega-3 long-chain fatty acids (which I had never heard about)-docosahexaenoic acid and eicosapentaenoic acid. And he gave me standard samples that I could bring back home and identify that these were high in Eskimo blood. And we published that in the American Journal of Clinical Nutrition.

At the same time, in the early 70s, Swedish and British researchers found out that prostaglandins that regulated blood clotting could be generated from omega-6 fatty acids. And suddenly we got the idea: What if, from our omega-3 long-chain fatty acids, there also would be generated prostaglandins that regulate blood clotting at another level (from a land-based food, polyunsaturated diet)? So we wanted to answer that because we had a lab able to do that in Britain.

We ended up finding out that prostaglandins coming from eicosapentaenoic acid did not promote blood clotting to the extent of omega-6. We published that in the late 70s and from there on-that moment, that paper in The Lancet-the interest in omega-3 polyunsats started, but rather slowly. It has been sort of a disappointment how long it has taken the medical community to divert from medicine to nutrition.

JB: Yes, and I think there has been, always, the pushback of nay-sayers who don't want to accept new discoveries. They will say things like, "How do we know the Greenland Eskimo would not have died because, basically with other causes of death, they must have a lower/shorter life expectancy. It is a harsh climate." Or, "How do we know they didn't die of something else, like strokes, so their heart attacks are low but maybe their cancer or stroke rates are high?" So you get all these secondary questions that obscure the primary observation. How did you deal with some of these other questions?

Epidemiological Data Confirms Early Findings

JD: Yes. We had to deal with them in an experimental way. The medical community has already dealt with them in epidemiological studies-major studies from the US actually document it. I am now thinking of, for example, the Nurses' Health Study from the Boston area from Dr. Willett's group. They came up with epidemiological data showing that nurses who had a high consumption of omega-3 did not have bleeding, but rather had a low incidence of thrombotic episodes, which supports the idea that we brought forward.

JB: It is my belief-and I've said it in a number of presentations that I have given over the years-that

your discovery is as important to public health as any singular discovery that I have heard of in the area of nutritional medicine. Certainly it is worthy of the Nobel Prize. It is interesting to note that Dr. Samuelson at Karolinska won a Nobel Prize for his discovery of the prostanoids that derive out of the arachidonic omega-6 family. I am wondering why you feel (philosophically) the fathers of all this work haven't been seen by the Nobel Committee to have the same degree of importance because it seems to me that this discovery of Samuelson on prostanoids really is more amplified in importance because of your discovery.

JD: Yes, but of course, they were the first to show that from polyunsats belonging to the omega-6 family, there were generated prostaglandins that regulated hemostasis. Then we made sort of a parallel thing. We said, "Couldn't it be so that another family of prostaglandins could do the same thing but in another direction?" And we managed to prove this. It is maybe fair enough that those who got on that trail first were the ones that got the laureate. Thank you for suggesting the idea, but I think that's the reason.

Heart Rate Variability

JB: Let's, if we can, follow on with the importance of your discoveries, because I think it plays out in so many ways in health. I know you have looked at things like heart rate variability, which I find is a fascinating surrogate marker for an indicator of cardiovascular function and how EPA and DHA play a role in heart rate variability. Could you tell us a little bit about that?

JD: Yes, and not only heart rate variability, but also heart rate. There were two major studies performed during the 1990s-the DART Study and the GISSI Study-giving omega-3 (either fish diets or omega-3 supplements) to patients who had had a coronary event, showing that in the groups given fish oil supplementation, the sudden cardiac death rate fell dramatically (up to 45{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in the large study which included more than 11,000 patients).

Sudden cardiac death is due to fibrillation of the heart, so we speculated about whether omega-3 fatty acids in any way had an influence on the heart beating/rhythm. An indicator of proneness to cardiac fibrillation and sudden cardiac death is your heart's ability to change its rate, its adaptability to stress and rest and functional demands. And this can be measured by putting a record on your heart for 24 hours, which we did in several studies, and found that we could improve heart rate variability in patients who had had a coronary heart attack.

To me, as a professor of nutrition, even more interesting was that if we took Danes who were normal, healthy, young males and measured their heart rate variability, we could improve that by giving them fish oil supplementation. This indicated that our Danish diet (which is far richer in fish and omega-3 than the American diet, on average) was below the optimal level.

JB: So that raises the question: What is the range of optimal level of intake of EPA and DHA? I know you have said that you can't just get there by cutting out omega-6s, you have to have adequate levels of omega-3s. What do you find?

Is There an Optimal Range for EPA and DHA Intake?

JD: Yes, there has been a lot of talk about the range between omega-3 and omega-6, and of course this can be used as a measure, but range means that you can also determine the range both by the denominator and the numerator. And, of course, you cannot improve the amount of omega-3 by decreasing the amount

of omega-6. Even if we have (maybe) too high a consumption of omega-6 fatty acids, it is still necessary that you feed your system the omega-3s because you can't make them yourself. And what is the optimal range or level? To be honest, we do not know. What we know is that 1-2 grams a day does a lot of benefit. So today we'll say that this is a good dosage to aim for.

JB: Can we go back, just for a second, to your extraordinary discoveries about heart rate and heart rate variability? We have often talked about the fact that as people get sicker and they lose function, their physiological degrees of freedom are diminished. In fact, in a hospital, the worst kind of EKG is one that is totally rigid and has very low variability. In fact the most simple EKG is a flat line, so as an EKG gets more simplistic, you are moving towards less physiological degrees of freedom. That bears on the whole question of how something like essential fatty acids (or the omega-3) can improve physiological degrees of freedom across many different disease states, not just vascular disease. So could you tell us a little bit about the discoveries and things like neurology and rheumatology and endocrinology?

Functional Aspects of Fatty Acids

JD: Of course, but first I want to stress what you just said. These fatty acids are built into every cell membrane in our body. They aren't there just for fun; they are doing something. What they are doing we do not know in great detail yet, but we are starting to have sort of a sense of it because it modulates the cell membrane's flexibility and it modulates the functional spots in the cell membranes-the ionic channels and things like that. And besides that, they have functional aspects of themselves. For example, in the brain and in the retina, DHA has functional aspects. Our brain is rather rich, and our retina is very rich, in DHA. It has been interesting to follow that. Deficiencies in long-chain omega-3 fatty acids are associated with disorders in our nervous system, for example, depression, Alzheimer's disease, and ADHD in kids. Also, intervention trials have proven that there could be a therapeutic effect of giving it to people with these types of disorders. Rather recently, the Framingham data study group published their data on Alzheimer's and found that what corresponds to a daily intake of .180 milligrams of DHA is associated with a 47{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} less risk of developing Alzheimer's in elderly people over a 9-year period. This is not an intervention trial; this is observational data. These are rather solid data that I (as a nutritionist) have enough from to base my recommendation to the public because I know I'm not doing any harm; I'm increasing beneficial effects.

JB: So when people hear this it sounds overwhelmingly persuasive that we should be doing something to improve our omega-3 intake. For a lot of people fish is either not accessible all year long or they don't like fish, so what do they do?

JD: As a nutritionist, of course, I always start with the diet (rich in fish, having 2 or 3 servings a week). This is related to a lower rate of coronary heart events. But then, if you can't buy the fish or if you don't like the fish (there are a lot of taste differences-personally, I love fish), the only way is to buy good quality supplement capsules or liquids and add that to your health maintenance in a daily amount of 1-2 grams (in prophylactic terms, for a normal person).

JB: So when we talk about high quality-I think that term, for a lot of people who may be unfamiliar with the process may be nonspecific-what kind of things in quality do we actually look for when we talk about fatty acid supplements?

Concern about Pollutants in Fish

JD: High purity. No oxidation. No level of toxic pollutants. Unfortunately, we know the human race (mankind) pollutes a lot, even the seas, so some fish will have a high level of pollutants (mercury, dioxins-you name it), depending on where they come from. I'm not saying that fish (in that aspect) is unhealthy, but, if you go for the fish oils, you can meet products that do not qualify as good and reasonable products. I always advocate to my patients to not take the cheapest offer; go for quality-things that you know are good. I, myself, have always had relationships with good producers (I'm sorry I can't name names).

JB: When we look at these fish oil supplement products, I note that they come in two kinds of general forms. They come in a triglyceride form, which would be considered kind of your normal dietary form, and then they have ester forms-ethyl esters, methyl esters, etc. Is there any difference between these two that you are familiar with?

Different Forms of Fish Oil Supplements

JD: Yes, chemically, great differences. When you eat a fish or a seal (we don't eat a lot of seals you and I, but the Eskimos did), it is in a triglyceride form, which is a natural form of fat that we absorb; they are ingested, split by the enzymes in the intestine, and absorbed as monoglycerides and as free fatty acids. These products contain a medium amount of omega-3s. You can enrich those triglycerides to improve their content (chemically) so that instead of one there will be two omega-3 fatty acids in the triglycerides. To me that is a reasonable way to make supplementation.

You can do it in other ways. You can isolate the fatty acids as free fatty acids and they are well-absorbed. The thing with the free fatty acids is that they are rather odd tasting; they are rough to take. Quality oil is actually low in free fatty acids. In the mouth free fatty acids can form soaps, so they do not have the best taste and therefore compliance (in my studies) was not good using free fatty acids. And then, again, you can make ethyl esters, which is a chemical derivative of a fatty acid that is not as well absorbed, but is reasonably well absorbed. These are the products you can use.

JB: One of the things I'd like to appeal to you (as an expert in the field) to help us to understand from the vast experience that you have had, is why you think it takes so long for something that seems to have such reasonableness associated with it (with so many studies-epidemiological, animal, human, intervention trials…) to finally have stickiness. Do you have some sense as to why this is so?

JD: To be honest, I have to blame my own profession (the doctors) because nutrition is not of high esteem and it is not an essential part of the education of a medical doctor. It has been rather a low priority thing for a doctor to deal with nutrition. A doctor likes operations and medication, prescribing a pill (which, of course, is what he is there for and should do for disorders, but in prophylactic terms, I think nutrition has a far higher impact and is far more essential).

The thing with nutrition is that it is not a part of the doctor's education process, and the impact from the pharmaceutical industry has put nutrition at a lower esteem level than pharmaceutical intervention. To be honest, I think that is simply the reason, but-again-I see a conversion. I see that the nutritional aspect of medicine is gaining impact nowadays.

JB: There are obviously myriad questions we would love to explore with you, but because of the limited time I will just ask one last question. You are speaking now, principally, to professionals who are dealing with patients everyday and are making decisions or helping those patients to make decisions

about their life. If you were to send a message to them from your 40+ years of experience, what would you like them to know in terms of takeaway?

JD: That the Western diet has been unbalanced with respect to the 2 components of essential fatty acids essential in our diet. This has been in favor of the omega-6. Besides many other things to consider in nutritional learning (to keep a good body weight, to refrain from drinking too much alcohol, to refrain from smoking, and to keep our physical exercise up), you should also be aware that you should increase your intake of omega-3 fatty acids.

JB: Dr. Dyerberg, I want to thank you both for this time and for the 40 years of hard work and diligence in helping us to understand this very important concept.

JD: Thank you. It has been my pleasure to be here in your lovely city.

What was your takeaway from this extraordinary discussion of Dr. Dyerberg's discovery with Dr. Bang? Of this Eskimo connection with low cardiovascular disease to their dietary omega-3 lipid intake? My takeaway is that this is a dramatic example of the power of nutrigenomics-a new model that is emerging in medicine that will frame a new therapeutic paradigm as we move into the remainder of this 21 st century.

There is a dynamic two-way interaction between nutrition and the human genome. This interaction determines genetic expression and the metabolic response ultimately affecting an individual's health status. These molecules that are found in diet have been sieved and screened through the laboratory of natural selection over millennia.

What Dr. Dyerberg really recognized in this study was that the diets of these Greenland Eskimos that contained these high levels of omega-3 fatty acids were somehow speaking to their genes in such a way as to create an outcome called lowered cardiovascular incidence. They, in part, were genetic expression modulators.

Since the 1960s, considerable work has mounted concerning this concept of dietary lipids and gene expression. One recent paper that speaks to this, demonstrating how the field is advancing, appeared in the *Proceedings of theNational Academy of Sciences.* It is a very interesting paper that describes how omega-3 fatty acid, docosahexaenoic acid (DHA), attenuates endothelial cyclooxygenase-2 induction through modulation of kinases-these signaling pathways that control gene expression, in this case Protein Kinase C Epsilon (PKCε).[26] You'll notice I've just gone back 180° to pick up what we were talking about earlier in this issue of *Functional Medicine Update*. Our diet contains constituents that speak to our genes in such a way as to regulate function through intercellular signal transduction. This process is mediated through the cell by way of these relay-race runners we call kinases. By modulating the kinases through receptors that sit on the surface of cells that pick up the information from our diet and lifestyle, it then causes the genes to read different chapters in the book of life, different stories. In this case, omega-3 DHA causes the cells that are inflammatory in nature to read a story called anti-inflammation by upregulating the synthesis of cyclooxygenase-2. So I think we are starting to see some very interesting underlying mechanisms put to the long-respected association between certain dietary principles and lowered incidence of chronic disease, making these seem as molecules of tremendous potential (both safety and effectiveness) in modulating function over years of living.

This concept that nutrition is a key environmental factor in the pathogenesis and progression of diet-related diseases takes us beyond nutrigenomics into this whole concept of cellular signaling. We said earlier that the type 2 diabetes, or obesity, or heart disease condition is preceded by altered cellular signaling that occurs years-maybe even decades-before an individual actually gets the disease and is diagnosed (and then given a drug as a prescription). In an article that is titled, "Dietary Lipids and Gene Expression" (this appeared in *Biochemical SocietyTransactions*), the authors describe how modulation of proinflammatory signals occurs by eating molecules in our diet that signal anti-inflammatory processes. [27]

Another example of this that you may be familiar with is the mounting evidence that vitamin D is more than just a bone vitamin; it is an environmental factor influencing the whole of the immune system, including the effects on inflammation and autoimmune disease prevalence. In a recent issue of *Experimental Biology in Medicine*, the authors of a review discuss the increasing evidence pointing to a link between vitamin D and autoimmunity, with increased vitamin D intakes decreasing the incidence and severity of autoimmune disease. [28]

In fact, we recognize that this particular association has to do with the increasing level (or activity) of 1,25-dihydroxyvitamin D3 (or cholecalciferol), the hormonal form of vitamin D in the blood, which is produced from 25-hydroxyvitamin D, and that is what we should be measuring in the blood of patients to maintain (or assess) the level of sufficiency of vitamin D.

We would like that 25-hydroxy level in the blood (25-hydroxyvitamin D3) to be at a level that is considered ideal or optimal, which is in the area of 80-120 nmol/L. If you are doing a vitamin D assessment in your patient, you would like the level to be between 80 and 120 nmol/L. To give you an idea of what that means, if your lab is reporting the data in nanograms per milliliter, that is 32-48 ng/mL is that equivalency (of 80-120 nmol/L). We like to think of getting our patients up around 50 ng/mL of their vitamin D hormonal 25-hydroxy form. You can do that by both administering higher levels of vitamin D and following their 25-hydroxy serum level, and also give them simultaneously the soy isoflavone, genistein.

Now why is that important? Because it appears that genistein upregulates the enzyme that is responsible in the gut mucosa for producing 25-hydroxyvitamin D, and it downregulates the expression of the enzyme that is responsible for detoxifying (or metabolizing) the 25-hydroxy D. So if you want to increase your 25-hydroxy D metabolism, the combination of genistein plus vitamin D can be helpful. This comes from a recent paper in the *Journal of Nutrition* (a supplement edition).[29]

This may, in part, explain why women who ate a traditional oriental diet didn't have high levels of bone loss and osteoporosis until they started eating a more Westernized diet. Although they got low calcium (they weren't dairy-product consumers, but they got adequate calcium), they got high vitamin D from fish and high soy isoflavones that activated calcium-binding protein and the effect 1,25-dihydroxyvitamin D3 has as an anti-inflammatory (reducing inflammatory signaling on the bone remodeling unit-the osteoclast).

Vitamin D Status and Colon Cancer

We also recognize that 25-hydroxy D is important as expressed in human vascular smooth muscle cells. It is very important in maintaining proper anti-inflammatory activity in the vascular wall and is also

activated by the presence of genistein. We know that same thing holds true in colon cancer cells. In fact, statistical evidence suggests that one of the major risk factor reductions can occur in colon cancer by improving vitamin D status. I'm now quoting from a recent paper that appeared in the *Journal of Endocrinology* in 2006 that talks about the fact that genistein, as a phytoestrogen, regulates transcription and translation of vitamin D receptor and lowers colon cancer incidence. [30]

In fact in a more recent paper in the *Journal of Nutrition*, talked about nutrients that regulate colonic vitamin D system and the relevance for human colonic malignancy, and how the proper vitamin D nutriture and epigenetic control of the hydroxylase enzyme, by having adequate soy isoflavone genistein present, can lower the relative risk of colon cancer. [31]

Vitamin D Status and Prostate Cancer

In addition, in a *Molecular and Cellular Endocrinology* paper, authors showed that genistein potentiates the growth inhibitory effects of 1,25-dihydroxy D3 in human prostate cancer cells, and, therefore, it is not just vascular endothelium and it is not just colonic cells, it is also prostate cells that all seem to really benefit from proper vitamin D hormonal signaling. [32] And then, of course, a more recent paper than these appeared in the latter portion of December 2006 in the *Journal of the American Medical Association* titled, "Serum 25-Hydroxyvitamin D Levels and the Risk of Multiple Sclerosis." [33] This article describes a prospective, nested, case-controlled study among more than 7 million US military personnel who had serum samples stored in the Department of Defense Serum Repository. The authors examined whether there was an association between multiple sclerosis cases identified through Army and Navy disability databases from 1992 through 2004 and vitamin D serum 25-hydroxy levels. What they found was that the results of the study suggest a high circulating level of vitamin D as 25-hydroxyvitamin D was associated with a lowered risk of multiple sclerosis, a neurological inflammatory disorder.

You'll notice there is a theme-about signaling molecules that are present in the diet that have been sieved through natural selection over years of living. In the pharmaceutical world, what we are starting to see is an attempt to try to find molecules that will alter these fundamental cell signaling hubs that regulate gene expression, inflammation, and the risk to chronic diseases. A review appeared in *Nature Reviews* in 2006 that I think is quite profound (related to this association) was titled, "PI3Kγ Inhibition: Towards an 'Aspirin of the 21 st Century?'" [34] **What the authors talk about is that these PI3Kγ** inhibitors are promising drug targets for the management of inflammatory disease. If you actually page through this article, you'll find a magnificent diagram that describes how many different disorders are associated with altered PI3Kγ activity-things such as sepsis, cutaneous and systemic anaphylaxis, allergy, chronic obstructive pulmonary disorders, stress remodeling and heart failure, thromboembolism, and lymphocyte chemotaxis abilities related to immune dysfunctions. All of these have something to do with inflammatory relationships and diseases like systemic lupus erythematosus, atherosclerosis, pancreatitis, asthma, allergy disease, hypertension, multiple sclerosis, and chronic obstructive pulmonary disease. All of those are associated with dysfunctions of the signaling pathways of PI3Kγ , so the pharmaceutical industry is out searching for new-to-nature molecules that can modulate the cell signaling across this range of clinical applications.

When we have screened constituents from nature foods, we have found there are many natural PI3K γ inhibitors (or modulators). We call them selective kinase response modulators that can (and have, historically) done this by the consumption of diets that are rich in phytochemicals. So, we ask, where are

the best molecules for the management of chronic problems, before they become acute? Could it be that we have taken these things out of our diets and lifestyles and added, in their place, things that stimulate altered kinase signaling to produce the trajectory toward the pathologies we see? Before you step across the street, and the sign says "Walk," let's make sure we know where we are walking.

Indole-3-Carbinol (I3C) and Diindolylmethane (DIM)

Going back, if we could, to hormonal effects in menopause, this raises the question, doesn't it, about the brassica vegetables or the cruciferous vegetable glucosinolates? One of those glucosinolates that alters cellular signaling is called indole-3-carbinol (I3C) and there have been some very interesting questions as to whether I3C can reduce changes in cervical intraepithelial *in situ* neoplasia. It could be that extrapolates to other food components that modify cellular signaling.

There was an article published recently in the *Journal of Nutrition* in 2006 in which the author, Karen Auborn, talks about how I3C and its congener, diindolylmethane (DIM), derived from cruciferous vegetables, help modulate insulin metabolism and insulin signaling by reducing both the 16-hydroxyestrogens and other proinflammatory estrogens, including the 4-hydroxy, at the expense of making more of the 2-hydroxyestrogens, which are antimitotic and not proinflammatory. [35] By eating more cruciferous vegetables, women can modify their hormonal metabolism. Maybe some of the problems women have with estrogen is not estradiol, estrone, or estriol, but is related to these altered estrogen metabolites-these hydroxylated estrogens (the 16- and the 4-hydroxyestrogens). Maybe these problems can be reduced in their severity and concern by consuming indole-3-carbinol or diindolylmethane.

This same argument, by the way, would hold true for males with prostate-related problems. There is emerging evidence to suggest that some prostate difficulties are associated with altered estrogen metabolism in males, as are breast problems associated with altered estrogen metabolism in females. In an interesting paper that appeared in *Integrative Cancer Therapies* titled, "Targeting Multiple Signaling Pathways as a Strategy for Managing Prostate Cancer: Multifocal Signal Modulation Therapy," the authors talk about these kinase regulators that are found in foods, like the glucosinolates. [36] These kinase regulators can modulate multiple kinase pathways that send appropriate signals to the genes that downregulate mitotic effects, cell cycling, cause DNA repair mechanisms to be enhanced, produce antioxidant effects that lower DNA damage, itself, and improve metabolism of hormonal messengers that cause cellular division.

You'll notice we are seeing a change in our thinking of one molecule at a time for one condition (which has been the nature of pharmacology) to multiple molecules to modulate complex pathways that then regulate cellular signaling and ultimately gene expression and cellular function. We have been controlled this way, historically, by way of the diets we have eaten. Foods contain complex ingredients that modulate these functions, no one of which works as a drug that powerfully, but together, they synergistically function by modulating these hub-like signaling pathways that we call kinases. I think it is a dramatic change in our thinking.

When we look at the whole story of hormonal effects and with the ever-increasing number of postmenopausal women, we are seeing more and more the question as to what hormones to replace. What should I be using? Bi-Est? Or should I be using Tri-Est, or transdermal estradiol, or testosterone and progesterone replacement therapy (these are the bioidentical hormone replacement therapeutics)? Each of

those has a role in the medicine of our future, but before we go there, there is this whole question as to how diet and lifestyle modulates the hormonal production, metabolism, receptor sensitivity, and ultimately cellular signaling. I believe that as we gain more insight into this topic, we are starting to see that the first stage of intervention should be that of modifying diet and lifestyle, because across every one of these chronic diseases, when put head-to-head against drugs or other therapies, these have proven to be more safe and more effective in modulating these chronic, early-stage problems that we associate with age-related diseases.

I think this is the emergence of an amazing new chapter in pharmacology. Rather than just looking for molecules that block one endpoint and create, then, a single variable outcome, we are looking for complex arrays of molecules that hit (much more gently) multiple pathways, manipulating their function, and creating a stability or a modulation of gene expression that then normalizes their function.

The analogy I often think of is the difference between monoculture, as a form of agriculture, and the complex rainforest. In monoculture, which is basically one crop over tens of thousands of acres, one bug, one blight, or one drought can jeopardize the whole of your ecosystem. You have to constantly shore it up with fertilizers, biocides, pesticides, herbicides-all sorts of things-to keep that crop stable. In the rainforest, which is very diverse, with multiple pathways going on all the time and multiple species, what you have is a stabilization of function. If one species is under jeopardy, others can take its place. There are many different tributaries for function to maintain stability. And that is the way we have evolved (our physiology) over time: multiple pathways, each one contributing a little to the overall symbiotic/synergistic balance, and the diets we have eaten are complex molecules that speak to those processes to lead normalization of function against the changing environment.

I hope as we close this issue of *Functional Medicine Update* and we consider the wonderful comments of Dr. Dyerberg, we see that we are witnessing a change in the direction, the path, and the future of medicine. And as the "Walk" light comes on and we start across the street, having looked both ways, I think we'll find that the landscape on the other side of the street will be very different, leading to a much more effective and safe form of therapy for chronic, age-related diseases.

Thank you very much. We'll look forward to visiting with you in April.

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