May 2008 Issue | Hasan Mukhtar, PhD Helfaer Professor of Cancer Research

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Welcome to *Functional Medicine Update* for May 2008. It is interesting and paradoxical that we're told to "just say 'no'" to drugs, and yet we seem to be the most medicated society that the world has ever seen. It seems like an interesting contradiction. For me this point was really brought home when I read a recent report. I was-I think-incredulous. I couldn't believe that it was really true, but it had been brought to me by some of my most trusted colleagues. They said, "Jeff, are you aware of the fact that in surface waters in the United States you can now find a whole array of pharmaceutical drugs by just sampling the water we drink?" And I said, "Come on, that's got to be an exaggeration. I don't think that that is true." I guess I shouldn't have such a degree of skepticism when I'm listening to friends I trust because I went to the literature and there are some very interesting reports from highly responsible and capable analytic chemistry groups looking at the level of pharmaceutical compounds, both the direct compound and their metabolites, in surface waters, not only in the United States, but in Europe as well.1

Admittedly, the levels of these substances are very low and the technology we have available today is much more sensitive to picking up very low levels, but I think it still raises an interesting philosophical question about over-the-counter and prescription drugs: where do they go? We don't metabolize drugs like we do food, where we burn enough to carbon dioxide, water, and urea, and some phosphate salts, and so forth. In terms of pharmaceuticals-because these are new-to-nature molecules that the body is not used to metabolizing-their excretory products (their metabolites) may be persistent (like with pesticides, where DDT gets converted to DDE, but DDE can stick around for a long period of time because it is not readily metabolized by microorganisms). Is there a difference between natural substances (to which our body has been exposed and developed metabolic and excretory pathways to manage over time) and new-to-nature molecules that our body is trying to manage through cytochrome P450s and conjugases resulting in excretory products that are different from what we see excreted after consuming nutrients from food?

I think this question kind of sets the tone for the topic we are going to speak about today. We are going to have the opportunity to visit with a researcher of the month who has over 30 years of experience in the field of phytochemistry and who has one of the most impressive publication lists that you can find in the academic communities in America today.

We had the privilege of recently speaking with Dr. Mary Ann Lila from the University of Illinois. She discussed the extraordinary work that she has been doing with her group on the role of various phytochemicals as genomic modulators of expression and how this relates to functional changes in the organism who consumes these phytochemicals. Following on that theme, we are going to hear from Dr.

Mukhtar this month, the person who first discovered the active principals in green tea.

Nowadays, everybody knows about EGCG (epigallocatechin gallate) and the chemopreventive effects of green tea. The socialization of this concept is interesting. People will feel good-feel that they have done the right thing-if they have their cup of green tea each day (no matter how stressful their life is and no matter how bad their diet is, if they had their cup of green tea, or even their green tea soda, they feel like they have done something good).

Public awareness about green tea derived from the fundamentally solid work of Dr. Mukhtar and others who followed on from his discovery. Dr. Mukhtar has had an extraordinary footprint in the whole area of phytochemicals and chemoprevention and the roles they have in physiologic function. We'll hear more later, but I just wanted to set the context by talking about this pharmaceutical concept: antibiotics, anticonvulsants, mood stabilizers, sex hormones, and anti-inflammatories have been found in drinking water. This impacts the water supply of at least 41 million Americans according to an Associated Press report in March of 2008. [2]

Again, concentrations are low, but if we look at 24 major metropolitan areas, measurable quantities of hundreds of different pharmaceutical compounds and their metabolites are found in drinking water. I think we can say that no one really knows whether this is or is not a problem. Low levels of hormetic substances, as we have described, can have significant impact on function if they happen to influence very critical switching points (or nodes) within the genomic expression profile or the metabolic profile (the metabolome). Sometimes small amounts can have big effects. In fact, in some cases, this is probably where the biggest impact occurs on physiologic function--hitting these more sensitive switching places within our intermediary metabolism (the metabolic nodes, or what I sometimes like to call, euphemistically, "the metabolic acupuncture points," the places that are most sensitive to modulations).

We really just don't know what effects low levels of complex arrays of these molecules and their metabolites have on cell function. We know (on marker organisms like phytoplankton and organisms in the aquatic ecosystem) that the effects appear to be real, but then we are not so sure-as it transfers up through the food chain-how that influences (if at all) humans. I still think it is alarming (probably a good word) to think that 62 major water providers, when tested, showed a number of compounds above the level of sensitivity of the methodology. Clearly, this concern will increase over time if more medications are used and we depend on pills as solutions.

Before the age of pharmaceuticals, we depended on what has been called by Hippocates the "food-as-our-best-medicine" approach. How does that approach differ in terms of both physiological function and ecological sense of balance? If we consider a phytochemical that is present in a food that the body has been exposed to for millions of years, the metabolic path for its detoxification and its ultimate effect on the biosphere has had the chance to be processed through the most lengthy laboratory experiment ever been done: natural selection. Organisms (including the top of the food chain-humans-and those lower on the food chain) have had a chance to become exposed to these compounds, and therefore there may be something very different relative to not only the individual effects of these compounds on the marker organism (in this case human), but also the secondary effects that it has as it has been metabolized and excreted and its persistence in the environment. Most likely it is not persistent and it has the ability to be used or metabolized by other organisms. This is what some people consider the difference between synthetic chemicals and natural chemicals. It is not only the influence they have directly on the organism,

but the secondary effects that they have through metabolism and on the biosphere when they are excreted.

When you talk to the general public, an assumption can be made that when something is excreted, it is out of sight and out of mind. We took it in. We got rid of it. It is gone. Forget about it. But if this is something that is persistent and doesn't have (in the environment) readily available metabolic pathways to detoxify it in organisms exposed to it in the biosphere, this persistence can lead to bioconcentration and accumulation, and it can ultimately affect offspring. We have seen this with xenoestrogens in the environment, certainly with DDT and DDE affecting the reproductive rate of birds. But now we are going beyond that to talk about pharmaceutical compounds and over-the-counter drugs, which may be having similar opportunity or potential for bioconcentration as a consequence of being in surface waters. This is a pretty remarkable step forward.

Transitioning from that, then, to the theme of today (which is to kind of contrast new-to-nature molecules that are used as drugs to natural substances that have biological activity, meaning biological response modifiers derived from natural substances), we are led to a discussion about chemoprevention (and even therapeutics) as it relates to these compounds in various health conditions. I think one of the areas that has received some of the greatest exploration, at least observational and clinical overview over the years, are those plants that contain active ingredients that have what has been called an adaptogenic effect on human function.

As a student of traditional pharmacology, I wondered early on what an adaptogen was. It sounded like a term that was almost just a buzz word or a catch word, not something generally understood within the field of pharmacology. But the more that I have had the chance to really gain a better understanding of what is meant by "adaptogen," the more I understand the power and also the support for that word. Let's look at what that means.

An adaptogen is said to be a substance that helps the body adapt to a changing environment or stressful situation. This could be emotional stress, chemical stress, or heat stress. I guess you would say an adaptogen increases the resiliency of the organism (the so-called organ reserve capacity of the organism) to maintain homeostasis against a changing environment. Are there any examples we can pull out that would actually support this concept of adaptogenic substances? The answer is "yes" because when we talk adaptogens, what we are really talking about are molecules that interact with receptor sites or with various signaling processes in such a way as to, at low levels of stimulation, enhance or serve as agonists, and at high levels of stimulation of a specific pathway, lead to antagonist of that pathway. So this agonist/antagonist activity gives rise to kind of a schizophrenic personality of that molecular species, which then induces this adaptogenic capability, meaning a capacity to maintain homeostasis or homeodynamics against change. So if there is a low stimulation of a specific process, this compound may stimulate receptor-binding and activate the pathway (that way it is an agonist). Or if there is a high level of stimulation with many things sitting on the receptor site that are activating that pathway or that process, this substance can then serve as an antagonist for that receptor activity and could downregulate the function in a hyperfunctioning state, and therefore it would be seen as having this dual personality: depending upon need, it would lead to normalization of function. That is what we mean by an adaptogen.

Examples of Adaptogens

In the plant kingdom, many substances have been found to have this characteristic of agonist/antagonist activity (or what I am terming "adaptogen"). The best examples that probably come to mind are the

isoflavone families of molecules that are found in soy or in red clover. We know the soy isoflavones (genistein and daidzein) have the principal effects of interacting with estrogen receptors to some extent, and as a consequence they can either stimulate activity of the estrogen receptor when it is underoccupied with its ligand, or they can antagonize the estrogen receptor by blocking or preventing the binding with an estrogen stimulator like 17beta-estradiol. So they can be an agonist in one case (low estrogen) and an antagonist in another case (high estrogen), so they are adaptogens in that respect (normalizing estrogens mode of activity at the estrogen receptor). I think that is one commonly understood example, but there are many, many other examples that are now being explored and being discovered where there are compounds (bioactive materials) in plant foods that actually increase the regulation of these receptor activities.

Let's look at ginseng. For years, ginseng has been considered an adaptogen-to be both yin and yang in traditional Chinese parlance. Recently, pharmacogenomics and the antiangiogenic-modulating and storage-like activities of the active principals in ginseng have been studied and have been found to be, again, this agonist/antagonist-type of characteristic. I am now quoting from a recent paper in *Clinical Medicine* in 2007 in which it was found that Panax ginseng actives, the ginsenosides, have a very profound effect to either serve as proangiogenic or antiangiogenic compounds, depending upon the specific state of function of that system.[3] And they also can serve as a steroid receptor agonist or steroid receptor antagonist, and so they, again, can have this normalizing or adaptogenic effect. This may explain in part why many of these adaptogens seem to have a variety of clinical applications from modulating hormones, to modulating stress, to modulating oxidative reactions (meaning they are said to be antioxidants). They are said to have anti-anxiolytic activity. They are said to improve wound healing. They are said to be anti-ulcer. How can all these effects come from the same mixture of molecules? I think it has to do with the fact that these are mixtures within natural products. Although they may have remarkably strong specific interactions, they have weak potency. They have this ability to maintain metabolic degrees of freedom, whereas a new-to-nature drug has been screened for its very high affinity to certain endpoints and it has a very high potency, meaning very low IC_{50}. It kind of nails these things very hard. It's like driving the point home very strongly. These molecules that are found in nature, as a mixture, hit many things a little rather than a few things a lot. I think, as a consequence, you get a different mode of action, a different physiologic function. You get a different kind of molecular or metabolic degree of freedom. It maintains plasticity. That is what we would call adaptogen agonist/antagonist capability. It is an interesting and different kind of pharmacology. It still participates with molecular interactions and the ligand-receptor binding and how that interfaces with signal transduction and regulating expression of function, but it does so in a different way. A mixture of molecules may be a reasonably high affinity, but lower activity, hitting multiple sites a little rather than a few sites a lot. That characterizes both the difference in functional capability and also the difference potential in adverse side effects between these two classes of compounds. So it is not that one compound/class is bad (i.e. new-to-nature molecules) and one is good (i.e. natural-derived molecules). It is using the right set of molecules for the right application. If you want to hold on, own, and completely (without ambiguity) control and regulate a function, you probably want a high-affinity and also very potent molecule that comes out of the *Physician's Desk Reference* that has been screened very exhaustively by people who are very knowledge about these high potency molecules. The emergency room, the critical care center, or acute medicine probably really benefit from having an array of molecules that have come through this kind of a screening process. On the other hand, for individuals with chronic conditions in which there is no one single thing that is causing the problem, but rather myriad imbalances in their web or network of physiology, then maybe hitting many things a little (using a mixture of natural

products that have differing receptor interactions) is preferable to that of hitting a few things a lot. Again, it is using the right personality of the molecular species in order to produce the right effect.

What I have said is that these substances that are derived from food or natural products that have these characteristics (agonist/antagonist) are secondary metabolites from the plant; they come off the genes of the plant. Ginsenosides are synthesized by the ginseng plant based on its genome, just as we would say that flavonoids are synthesized off of the genes of the plant producing them, or proanthocyanidins coming out of berries, or catechins coming out of the tea plant, or the glucosinolates coming out of the cruciferous family of vegetables. These are all secondary metabolites produced by plants in response to what appears to be perceived stress that that plant is under, and so the plant upregulates these anti-stress compounds to be manufactured within its own biosynthetic capability.

When we look at glucosinolates, they have a specific function in the cruciferous vegetable family to help protect against predators. If we look at things like carotenoids and xanthophylls in plants, these photosensitizing pigments have the effect to protect against a stress called sunburn by trapping the sun's energy in such a way as to prevent singlet oxygen damage and free radical injury caused by excessive sunburn. If you can imagine having your arms raised to the sun all summer long in a cornfield in Iowa that would be a pretty difficult situation. Every morning, seeing that sun come up, you'd probably say, "Oh no, not another day." (Even with SPF50.) So the plants have these adaptive capabilities by upregulating their production of these phytochemicals to defend them against environmental stresses.

Data from Experiments with Cultivars

If we talk about the phytochemical composition of various fruits and vegetables, it is related, in part, to how they are grown. I was interested to see a paper in the *Journal of Agriculture and Food Chemistry*-this is in 2007-in which they were looking at the same cultivars of berries, some that were grown by traditional, what we might call "organic" agriculture methods, and another from the same cultivar in an agricultural system that used pesticides and herbicides and fertilizers that basically put the plant under pretty low stress (it didn't have to worry about defending itself).[4] And then they looked at the presence of these bioactive ingredients within the berries. Agents that were found to have influence on lowering inflammation (these were phenolic acids, anthocyanidins, proanthocyanidins, and also hypoglycemic agents). What they found is that the levels of these bioactive compounds-these secondary metabolites (phytochemicals) in the berries that were grown under the organic agriculture conditions (I mean stressed, obviously)--were higher in level per unit mass of the berries versus those that were grown under the less stressed fertilizer/pesticide/herbicide environmental conditions. I think we look at the value of our foods from the perspective of some of these native secondary metabolites and we have to ask, "How was the food raised?" and "What was the general content of the substance within the food?" not just "We know that a food has that phytochemical in it." We would have to ask something about its condition of growing and harvesting and storing and so forth, and so we would have a potential variety of different levels, depending upon those variables.

Notwithstanding all of that, however, I think you can see that what I am talking about is a different model for potential development of bioactive substances for modulating function from that of the traditional pharmacological model. We are talking about mixtures of molecules that are produced by plants naturally as a consequence of their defensive mechanism that then are consumed by humans in their diets or as natural product remedies, which then induce in the human a similar anti-stress response. As you might know from previous issues of *Functional Medicine Update*, from interviews with people like Dr.

Christoph Westphal from Sirtris Pharma, the term that is applied to this concept is "xenohormesis"-foreign substances (i.e. plant-derived secondary metabolites) having a hormetic effect (meaning small amounts having a larger effect on function)-again going back to this concept I talked about earlier of influencing the so-called metabolic acupuncture points and having influence on function far greater than one would anticipate based on just the mass of the substance alone.

The Clinical Application of Xenohormesis

Now let me give you an example of that from clinical application. Let's take a look at omega-3 fatty acid supplementation. We are told that it is good to consume about 1 to 2 grams a day of EPA (let's even say 3 grams, if you wanted to be on the good side of the equation here). So let's say 3 grams of eicosapentaenoic and docosahexaenoic acids (i.e. EPA and DHA). How does that really compare to the overall amount of fat that is in the body of a fairly fit and healthy individual? So let's take the example of a 170-lb. male who has 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} body fat. He would be pretty fit, pretty lean. And 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of 170 pounds is about 25 pounds of fat (about 454 grams per pound, so we multiply 454 times 25 and we come out with about (I'm going to rough it out) 10,000 grams, say, of body fat. If we were to look at that for a second (10,000 grams) and we say, "Let's see, we are consuming, as a supplement, 3 grams of EPA/DHA mixture a day-what's 3 out of 10,000?" It is a rounding error. You don't even see it. It is lost in the sea, right? And so you say, "Well, there's no real reason, then, to supplement with EPA because clearly it is of no significance relative to the massive amount of stuff that we already have in our bodies (the 10,000 grams of other fats). But see, this is where xenohormesis plays a role because as we bring in these important fatty acids, omega-3 fatty acids, that have an impact that is different than that of the whole body burden of fat. It has a hormetic (small amount, bigger effect) effect. And so this would be a specific example of how hitting at the right place by the right concentration with the right form leads to a larger metabolic response.

That theme holds true for a variety of potential substances in plant foods that could be hormetic that serve as chemopreventive agents-agents that help to defend against chronic, age-related diseases because they modulate function in such a way as to lead to adaptogenic response around a set point which is healthy physiology. That is one of the themes you are going to hear from Dr. Mukhtar as he tells his story, from the discovery of EGCG in green tea to now literally hundreds of other phytochemicals that have potential biological response modifying activities.

Let's look at traditional Chinese medicine, which is built on this concept of multiple agents in a complex mixture coming from natural sources and having impact on physiology, sometimes at a very low level. We even talk phytochemicals where the level of concentration is fairly small relative to, obviously, a chemically synthesized, purified single molecule drug. If we were to examine, then, from traditional Chinese medicine to rational cancer therapy, which was the topic of a paper in *Trends in Molecular Medicine* in 2007, we are led to recognize that many of these natural products and derivatives thereof belong to the standard repertoire that ultimately lead themselves into traditional cancer chemotherapy.[5] It started off in natural products, in nature as mixtures, and over time we get more and more to a purified, drug-like, single molecule. Examples include things like the *Vinca* alkaloids, the taxanes, and the camptothecins. In recent years, the potential of natural products from plants, notably from medicinal plants used in traditional Chinese medicine, has been recognized by the scientific community in the Western world, and there have been recent developments in this field which have allowed for comparison

of single molecules of high potency to mixtures of molecules of modest potency and the influence they have on various cancer cell models and tumor models in animals, trying to contrast the difference between chemoprevention and maybe chemotherapy.

Traditional Chinese medicine holds an important position in primary health care in rural areas of China. It is also appreciated in urban and well-developed areas for its 5000 year-old tradition. The Chinese government has undertaken enormous efforts to modernize traditional Chinese medicine (TCM) by investing in capital and every level of scientific and clinical research, and trying to better understand the underlying principle of TCM. Western interest in TCM stems from the hope that it might complement Western medicine by providing different tools for different applications. Medicinal herbs play a very important role in TCM, and even in Western medicine many of our medicines were traditionally derived from green pharmacy, or natural products. However, medicinal plants gradually, over time, have lost their importance as pharmaceutical agents as synthetic chemistry progressed in Western countries entering the 20^{th} century. We got to the point where single molecules became the dominant theme because it was easier to test a single molecule against a single end point using the double-blind, randomized, clinically controlled trial. Currently, there is seemingly a revival of interest in medicinal plants and an increasing scientific interest in bioactive natural products as chemical lead compounds for the generation of what might be considered semi-synthetic new derivatives. This would be where you would modulate or modify the natural product into a slightly different structure to make it a new-to-nature molecule that then can be patented and has maybe more financial growth and return-on-investment possibility. But we still have a very significant interest in the natural compounds that appear in the mixtures in their native state and how they influence function. At the pharmacological level, the different areas of classical pharmacy differ from this kind of view of TCM and the models that I was describing earlier: mixtures of molecules having smaller effect across many functions and leading to this hormetic adaptogenic response versus a hard-hitting single molecule producing a dominant effect on one pathway that has been screened for its ligand-receptor interaction. We start seeing some very interesting classical targets for these traditional Chinese medicine-derived materials.

People are looking at genomic relationships, proteomic relationships, and metabolomic relationships There is now a lot of very good science being done on the mixtures of these natural products that have come through traditional history-5000 years of history-and asking, exactly, how do they work? What is different about their role and function from that, say, of a single, new-to-nature molecule in chemoprevention or in therapy? I think we are starting to see some dramatic steps forward in this, and some of these are being found to be extraordinarily interesting products related to modulating what we call the inflammatory pathway.

As you probably know, the inflammatory pathway is really the inflammatory path*ways*. There is ever increasing recognition that inflammation is an underlying etiological contributor to virtually every age-related chronic disease-from such things as osteoporosis, coronary heart disease, arthritis, Alzheimer's dementia, thyroiditis, metabolic syndrome, type 2 diabetes, peripheral neuropathy, nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, even loss of muscle mass with aging through metabolic sarcopenia-all of these have an inflammation component. Dr. Claudio Franceschi has recently termed this "Inflammaging." Inflammaging is an interesting kind of conjoined term that talks about the relative increase in biological aging as a consequence of underlying inflammation, and that this connection between inflammation and biological aging connects, then, to chronic disease.

In a recent paper in an issue of the *Nutrition Reviews*, Dr. Franceschi says that this accelerated biological aging process that we now see as demonstrated through increased prevalence of various types of chronic disease has a very close connection with underlying inflammation.[6] Centenarians, when examined, have very low levels of proinflammatory materials. Centenarians are very unique because they have actually fairly high levels of proinflammatory materials, but what they have is even higher levels of anti-inflammatory responsive markers. It is as if they have a very vigilant immune system, but it has been kept in control by having these regulatory breaks that are called anti-inflammatory molecules that buttress the inflammation/anti-inflammation pathways. It is as if they have a robust, healthy, and responsive system to infection and offenders. It is not suppressed. It is not denied its function. They have got the right regulatory balance between immunological activators and immunological attenuators. This is all, I think, an interesting observation because we often say, "Well, we want to regulate the immune system; we want to activate the immune system; or we want to downregulate inflammation." But maybe what we want to do is make sure that we have the right balance between inflammatory and anti-inflammatory activities.

Neuroinflammation in the Aging Population

Clearly, one major area that is emerging to be very important in an aging population for this story is that of neurological aging. Neuroinflammation is becoming more and more recognized as a major concern. We recognize things like *Gingko biloba* have a whole variety of molecules in the complex mixture of natural products that modulate aspects of the inflammatory signaling process that might be selective to that of neurologic aging. But not solely neurologic aging, because we also see effects of *Gingko biloba* on liver function, reduction of liver oxidative stress, and inflammation. These constructs of mixtures of molecules from natural products that have unique effects on inflammation signaling is an emerging view in chemoprevention and what I might call chronic disease prevention.

What are the implications of neuroinflammation on the pathogenesis and molecular diagnosis of Alzheimer's disease? I'm now quoting from the *Archives of Medical Research* in 2008-an article that talks about cytokine production by the microglia of the brain.[7] The brain's immune system has a lot to do with the etiology of Alzheimer's dementia. The glial cells communicate through inflammatory mechanisms with the neurons to lead to these hippocampal fibrillary tangles (neurofibrillary tangles) and ultimately the beta-amyloid that undergoes the conformational changes that leads to plaque. This is an oxidative stress and inflammatory-related pathway.

We recognize that things like resveratrol (in peanut skins and in grapes) have an effect on pro-apoptotic effects and inflammatory effects. We recognize that that coupled together with the isoflavones that I discussed earlier (the genistein soy isoflavones) have very interesting roles as anti-inflammatory compounds that work synergistically. I am now quoting from a paper in the *Journal of Nutrition* in 2007 in which the authors demonstrated the extraordinary roles that resveratrol and genistein have in anti-inflammatory, anti-adipogenic, and anti-proapoptotic effects.[8]

We start to see complex interactions--it is not just one at a time and that is what makes this so difficult. That probably explains why things like omega-3 fatty acids (DHA and EPA) recently have been shown to improve cognitive performance among the elderly; we get mixtures of these molecules that influence complex physiological pathways that then lead to normalization of inflammatory pathway. I'm now referring to an article in the *American Journal of Clinical Nutrition* in 2007 about why an anti-inflammatory diet that is low in arachidonic acid and increased in omega-3 oils has been shown to be

helpful in patients with rheumatoid arthritis, or a diet that is low in gluten-sensitizing protein is helpful in patients who have various forms of rheumatoid arthritis.[9] I'm now actually quoting from papers that appeared in *Rheumatology International* in 2003 and *Rheumatology* in 2001.[10] Two years after a vegetarian diet that had higher levels of omega-3 fatty acids and was low in gluten was introduced to rheumatoid arthritis patients, there was improvement in joint mobility and reduced pain (that's *Clinical Immunology*, back in 1994).[11] And immunology of the gut plays a very important role in lowered inflammation--this is "Immunity, Inflammation, and Allergy in the Gut," a review that was in *Science* magazine in 2005.[12] This article shows that probiotics and prebiotics play a very important role beyond that of the intestinal tract in lowering inflammation, so this whole concept of gastrointestinal restoration (what we call the "4R Program"-remove, replace, reinoculate, repair) relates to delivering lower inflammatory potential through the gut mucosal immune system. I am quoting now from a "Probiotic and Prebiotic Influence on Intestinal Inflammation" article that appeared in November 2007 in*Nutrition Reviews*.[13] Even in inflammatory bowel disease there is now very strong evidence that probiotics can be very helpful, producing extra hepatic (extra intestinal) reduction of inflammation as a consequence of probiotic supplementation. The gut bacteria flora is another important part of this "Inflammaging" concept and maintaining proper gut-immune function. Gut-immune activating substances, for many people, may be things like food-sensitizing proteins (like gluten-containing proteins) that increase gut-mucosal permeability, encourage the release across the gut mucosa of potential larger molecules, and can induce, then, inflammatory response. In fact, in a recent paper that just appeared in *American Journal of Clinical Nutrition* it was found that a high-fat meal, in apparently healthy people, induced alteration in gut-mucosal immune function such that in the blood, after the meal, bacterial lipopolysaccharide was seen. This is a low-grade form of endotoxemia, and it was associated with an increased output from white cells of tumor necrosis factor-alpha. This is a very important paper for those of us who have been speaking for years about the gut connection to the rest of the body and how diet might influence inflammation. This is the *American Journal of Clinical Nutrition*, volume 86, page 1286 in 2007.[14]

So the diet can influence the immune system directly or indirectly through the immune system. The complex array of phytochemicals in the diet can have roles on this whole inflammatory signaling process and can be organ-specific or generalized in impact. That couples back to the concept of chemoprevention and even management of chronic disease using complex arrays (mixtures of molecules) that hit a lot of things a little, rather than one thing a lot.

So with that as a preliminary insight, let's now move to our clinician/researcher of the month, where you will really get the full story.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
Hasan Mukhtar, PhD
Helfaer Professor of Cancer Research
Director and Vice Chair for Research
Department of Dermatology
University of Wisconsin
Medical Science Center, Room B-25

1300 University Avenue
Madison, WI 53706

I am very pleased to have the opportunity to introduce our researcher of the month to you. I have been so fortunate over the last 27 years to speak with some of the world's most renowned contributors to the development of the functional medicine concept, and certainly this month is no exception. Dr. Hasan Mukhtar is our special guest this month, and he has a resume and background second to none. I have been following his work for more than 10 years as it relates to natural products and the effects that they have within cellular physiological systems.

As a Helfaer Professor of Cancer Research and the Director and Vice Chair for Research in the Department of Dermatology at the University of Wisconsin Medical Science Center, Dr. Mukhtar has authored and published more than 400 papers in this field. He is a paragon. He is an institution unto himself.

Dr. Mukhtar started his work in India, where he was involved with work on cytochrome P450s and detoxification. He did his postdoctoral fellowship at the Medical College of Georgia and worked at the National Institute of Environmental Health Sciences at Research Triangle Park. Ultimately he came to his present position in the Department of Dermatology at the University of Wisconsin. Dr. Mukhtar is just an extraordinary investigator. He has mentored many students that have gone on to do their own work and become leaders in the field.

I was very pleased to see that he wrote a piece for "Profiles and Legacies" at the request of the Journal of Cancer, Biology, and Therapy, which describes his background and his professional legacy.15 I think all of us wish we had as rich a resume and background as Dr. Mukhtar. His work on the editorial boards of 22 scientific journals in diversified fields including cancer, pharmacology, toxicology, biochemistry, dermatology, and photobiology is just kind of a snippet of the breadth of activities that he has had.

One of the things that Dr. Mukhtar has been very actively involved in recently (and we will discuss this) is his work on prostate cancer prevention and management by custom tailoring of a chemopreventive regimen and how that relates to things like various bioactive ingredients in foods and spices and modulators of intercellular signal transduction through cellular processes that these molecules are identified to have.

With all that as a very lengthy introduction, Dr. Mukhtar I really would like to welcome you to Functional Medicine Update and thank you for spending the time with us this morning.

HM: Thank you very much and I am honored to be with you. I really appreciate the kind introduction you gave me. I never knew I had contributed that much; that is nice to know.

JB: I think all we have to do is look at your resume for five minutes to know the amazing contributions that you have made. Let's talk, if we can, a little bit about how you got started down this pathway of looking at natural products and evaluating their effects in a different way than maybe previous investigators had done.

Obviously you had started off a little bit on this cytochrome P450 as a detoxification biotransformation

system, but how did it lead you into what now has turned out to be this extraordinary career?

Discovering the Health-promoting Effects of Polyphenols in Green Tea
HM: I was always fascinated with the idea of prevention of diseases. I came to understand that in order to prevent any disease we need to understand what actually happens. During that course, I was fascinated with the idea of looking at natural products because I was made aware that most of the drugs we use today are derived from natural products. It seemed to me that nature gave us these plant products (botanicals, vegetables, fruits) to enjoy, and then endowed then with many agents (products to discover)--that can prevent many diseases. So that is how I began my career in this particular area: nature's part in disease prevention. I began more than 25 or 30 years ago. Each time I looked into various systems, I found new things. Within the last 10 years, I think I was the first to show that polyphenols present in green tea may have some health-promoting effects. That work was started in 1988, from my lab, and it has become the talk of the town. "Green tea does this; green tea does that." Many of the biological and cellular processes we have found are modified by the green-tea-containing agents. So that is a brief introduction. How would you like to continue on from that?

JB: I think anyone who has read about nutrition at all, be they either in the science world or in the lay public, obviously has this green tea connection to health in mind. You only have to go to the refrigerator case of a supermarket and you see all these green tea products now that are coming out. If you are more science-based, you know about epigallocatechin galate and some of its effects and the whole nature of this discovery. What was the first discovery you made that kind of got you in to seeing some of the power that was within the composition of the green tea concentrate?

HM: We made many observations with green tea: that green tea can prevent cancer development in animal model systems, especially upon the skin. But most important of that, in my judgment, was our 1997 publication in the Journal of the National Cancer Institute, where we showed that you can take a polyphenol from green tea, EGCG (which you talked about a few seconds ago-epigallocatechin galate), and put it in a cancer cell (any kind of cancer cell).16 These cancer cells undergo apoptosis, and apoptosis is nothing but programmed cell death where cells make a decision to die. What good is there if it does the same thing to the normal cells? We took the normal cells and put the same amount of the EGCG in them, which are those concentrations that are physiologically attainable, and nothing happened to those normal cells. So this was the first distinction that any dietary or botanical agent was shown to make cancer cells commit suicide at a concentration where nothing happens to the normal cells. This became a paradigm for our research that has lasted for more than 10 years now. And now we know hundreds of compounds have a similar kind of biological effect.

JB: I have had the chance to read what I think is one of the most well-written reviews in this area that you authored (you were one of the principal authors), which appeared in Cancer Research in 2006 titled " Targeting Multiple Signaling Pathways by Green Tea Polyphenol EGCG," and one of the things that struck me (that a lot of people don't seem to understand) is that one of your discoveries is that these molecules that are present in these natural product mixtures target multiple pathways.17 It is not like a traditional pharmacology discovery. Could you tell us a little bit about this? I think this is very interesting.

The Importance of Targeting Multiple Pathways
HM: It has been made clear by many, many investigators, including us, in the last 15 or 20 years, that the

cancer cell adopts multiple pathways to survive and thrive. A single target agent is that you can kill or do something with that target, but the cancer cell is very clever. If that pathway is eliminated, it will adopt another pathway to grow and survive, so scientists have been looking for agents that can kill the cancer cell through many pathways. We have found that green tea polyphenols have the ability to target multiple pathways.

Let's say the cancer cell has 10 different routes through which it can survive (and I am not saying that it only has 10 routes). If you can only block one of these routes, there are still 9 routes to go. It has become clear that with most of these routes that cancer cells can adopt, green tea polyphenols are able to limit those. It looks like a jigsaw puzzle now: the cancer is trying to stay alive (if this pathway is eliminated, let's go to another pathway). The moment it goes to another pathway it says, "Alright, here is also a blocker." So this compound from green tea that we found can block most, if not all, pathways that lead to survival of the cancer cell. We say that it adopts a "multi-targeted" approach for inhibition of the cancer cell.

JB: I think how you (in that paper) summarize some very complex pathways--the inhibition of NFkB signaling, the inhibition of MAP kinases, the inhibition of epidermal growth factor, the inhibition of overexpression of COX2, the inhibition of proteozome, the inhibition of vascular endothelial growth factor, metalloproteinases, urokinase plasminogen activator-I mean this was a very nice review in a short summary of tremendous biology that has only been discovered in the last, say, 10 to 15 years.

HM: That's true. I am not aware of any other naturally occurring agent that is so versatile in making the demise of the cancer cell through inhibition of many, many pathways which you described a few seconds ago. So the cancer cell finds itself in a dilemma: "No matter what happens, I have to die." Let's say there are 10 roads through which you can go and there is a block in every single road. You cannot go anywhere else. So that is the strategy that a single agent-green tea-is doing, and we are now learning that there are many, many more agents that have the same kind of ability, and many more agents derived from natural products, especially dietary products, which have the same kind of ability. So if we can, I will come back to what you were referring to in the beginning-that if we can develop a cocktail of agents, ultimately, that if we identify let's say 20 different or 30 different pathways that are there which make the cancer cell survive, and let's say green tea is able to inhibit 10 of those and other agents are able to inhibit 5 of those, and if we can use different agents and develop a cocktail, I think we will win in the end, to a great extent, by inhibiting the march of the cancer cell from one stage to another stage.

JB: One of the things that you point out in your work is the remarkable discovery that these biologically active agents influence intercellular signal transduction and serve as kinase modulators through things like MAP kinases, the ERK J and K pathway, or through PI3 kinase. These seem like pretty remarkable, intimate relationships between the molecules and food and fundamental processes that translate outside information into inside genomic messages within cells and serve as transcription factors. Is this a fundamental discovery, do you think, that is changing our view in the biological sciences world?

Developing a Cocktail of Agents to Inhibit Carcinogenesis

HM: I think it is. Let's imagine all these pathways you describe (MAP kinases and proteozome and this and that) as a network. We don't know, really, how many of those are involved. Many of those have been discovered; many more will be discovered in the years to come. So it is a network of pathways that make the transformation of a normal cell to a malignant cell and, furthermore, the journey of the malignant cell

to become an invasive cancer. So if we can discover all these pathways (complex pathways), which we are discovering left and right every single day, then our job is to put breaks along these pathways so that we can devise agents (a cocktail of agents) which can inhibit the cancer development process. With this idea in mind we are trying to develop a cocktail of agents to inhibit the process of carcinogenesis through the use of simple and inexpensive agents derived from natural products.

JB: It seems very interesting to me that this is a philosophically different approach than that which has been seen in traditional pharmaceutical science, which is to take one molecule at a time and look at its very low IC50 high-potency activity on blocking a certain process. Here you are talking about mixtures of molecules that have more of a symphonic effect upon pathways of metabolic function. So it seems like a whole different strategy. Am I right in making that assumption?

HM: The idea is so simple. For some of diseases, there is a defined pathway. Unfortunately, for cancer, we have learned the hard way that that is not the case. It is a very complex process; hundreds of thousands of genes are involved, hundreds of thousands of pathways are involved. So how in the world we can think that a single drug can ever be developed for the treatment of cancer? And that is a major hurdle for the treatment of cancer, in my judgment. Most importantly, the cancer of one site (one individual) may adopt a different pathway to develop and survive and thrive, whereas in another individual it can adopt a totally different pathway. That is why one drug that may be effective in one individual may fail in another individual. If we can give a cocktail of agents that will work through different pathways it is likely to succeed more effectively than a single agent.

Research on the Prevention and Management of Prostate Cancer

JB: Let's move, then, from this kind of general discussion to some of the more recent, specific work that you have been doing on the prevention and management of human prostate cancer because that obviously is big area of therapeutic concern right now with the rising prevalence in males. I was reminded of another paper in 2007 from your group in Clinical Cancer Research on the combined inhibitory effects of green tea polyphenols and selective COX2 inhibitors and the growth of human prostate cancer cells.18 Tell us a little bit about how this is evolving, this cancer chemoprevention work that you are doing.

HM: Same idea, even with prostate cancer. Processes involved somehow damage to the normal cells. Inflammation is the key there. Through that, some kind of inflammatory lesions are produced that then develop and travel through different pathways to cause cancer in the individual, which can adopt a different pathway through which cancer migrates and metastasizes. My lab is actively identifying the pathways which are apparent in the development of cancer of the prostate gland, and how can we develop or identify nontoxic, dietary inhibitors which we can mix together and hopefully stop the growth of the normal cells to inflammatory cells to cancer and, subsequently, metastasis of the prostate cancer.

JB: So with that I am led to this most recent publication from your group that I have, which is in Chemical Biological Interactions, and is a 2008 publication talking about the prevention of prostate cancer through custom tailoring.19 In this paper you talk about the agents from, obviously, the green tea plant, and turmeric (which is curcumin), and pomegranate, and soy bean genistein, and cruciferous vegetables (indole-3 carbinol), and resveratrol from red grapes...

HM: Initially we put the idea out there because the cancer cell adopts multiple pathways to survive and thrive. If we can identify in an individual, through a genomic and proteomic approach, what kinds of

defects have occurred in genes (proteins, oncogenes, and similar response genes), then we have identified those genes and we can look up in our armamentarium of natural products and say, "Alright, you have 7 genes that are defective or 5 similar responses which have gone defective which are ultimately going to put you at the higher risk for development of prostate cancer." We can find out the agents which can destroy these defects.

So we need two kinds of information: we need to identify individual defects, and then we need to find what agents can fix those defects. Through that approach, we can make a customized cocktail and give it to individuals. This approach could be extremely effective in high risk individuals. Let's say one brother has prostate cancer, then the other brother is likely at higher risk. If the father has prostate cancer, then the son is at higher risk. Same thing for breast cancer. If one sister has breast cancer, the other sister is at higher risk. If the mother has breast cancer, her daughter is at higher risk. Can we identify high risk individuals and start identifying their genetic profile? If these abnormalities are detected early on, we can to do something to fix those defects. How can we do it? We can develop a cocktail of agents and, say, use curcumin, green tea, pomegranate, whatever it is, and hopefully that can stall the defects that are occurring in a person at higher risk and hopefully those defects are repaired before the damage has taken place.

JB: This is a very visionary concept: nutrigenomically based, personalized medicine or nutrition-that's a really powerful concept. Do you feel from your work that one could actually get adequate levels of these nutrients into their diets to be of therapeutic value?

HM: There's a long way to go. I think, ultimately, we can succeed. At this stage we have no idea, and that is why human variability exists. That is why more work has to be done. That is why the personalized cocktail approach could be more effective because we may not be able to deliver the concentrations of one agent that could be effective, but we can mix up small amounts of different agents. The whole concept is like the multivitamin concept. I want to bring a "multi" natural product concept.

JB: What do you think the next steps will be in making this become a clinically applicable concept?

HM: I think we have to develop a cocktail and test it in human individuals who are at higher risk. We don't have to wait until they develop cancer or not. We have to do some biomarker analysis, which are indicators of the likelihood of development of cancer. That is a multi-million dollar task. There is a long, long way to go.

JB: Have you seen any receptivity to this being funded by our granting agencies so that people see the value of this?

HM: Granting agencies look at things differently. There is a big barrier: to convince them because of the issues like availability (bioavailability), stability, interaction of one agent with another agent-those are the dogmas, those are the hurdles. I haven't seen a shift in the way the way the funding agencies look at it.

JB: We are very encouraged by the quality of the science that you are doing and perhaps acceptance will happen soon because it appears as if the model of treating things after you get them is not very efficient. I think the future, as you have described it, of nutrigenomic-based chemoprevention sounds to me like it has a huge amount to offer in the prevention and treatment and maybe management of these major

chronic diseases.

HM: Thank you very much.

JB: I want to thank you so much for spending this time with us. I believe your work has set the tone for all the rest of us in hopefully moving to a different strategy as we see the future unfold.

HM: It has been a privilege to be with you.

We thank Dr. Mukhtar very much for his extraordinary comments. What a tremendous contribution his work and that of his colleagues has made over the years in helping us to understand this whole concept of the mechanism of chemoprevention and biological activity from natural products and food-derived, secondary chemicals.

Traditional Medicine as Front-line Therapy for Millions of People

Traditional medicine has continued to provide front-line pharmacotherapy for many millions of people worldwide and so I don't think we should discount any of this as being kind of secondary importance; it has primary importance. Although application is often viewed with skepticism by the Western medical establishment, we know now that medicinal extracts used in ancient medicinal traditions such as Ayurveda and traditional Chinese medicine, are rich sources of therapeutic compounds for modulating function in areas of chronic illness. The transformation of traditional medicines into modern drugs has its origin in the archetypal examples of the antimalarial, quinine, and the antipyretic analgesic, aspirin, coming from willow bark. The *Vinca* plant was very important in developing and delivering various pharmacologically active compounds. The alkaline, quinine, was isolated in 1820 from the bark of several species of chincona and is thought to have been used by Peruvian Indians to suppress shivering since the 17^{th} century in the treatment of malarial fevers.

Similarly, we know aspirin was derived from salicylic acid and the bark of the willow tree, and used traditionally to treat fever and inflammation in many cultures worldwide for at least four millennia. The successes of these two early "blockbuster" natural molecules set the stage for ongoing discovery effects and efforts across the world with traditional medicinals. Compounds derived from natural medicinal extracts are appealing for several reasons: they are often stereochemically complex, multi- or macro-cyclic molecules with limited likelihood of prior chemical synthesis, and they tend to have interesting biologic properties. They have also been sieved through the laboratory of natural selection, so they have some history and relationship with our physiology. But perhaps most importantly, parent extracts have been clinically tested in this traditional milieu, in some cases over millennia, so there is this empirical understanding of their application.

Despite these advances, however, the path from traditional medicines to Western pharmaceuticals is fraught with challenges as a consequence of different philosophies I mentioned in the introduction of this month's *Functional Medicine Update*. We have a tendency to believe that new-to-nature molecules coming off the desktop of bench chemists, which show very high levels of activity (i.e. potency) are the preferable molecules to use because they have this supposed specificity and potency of action. However, as we have learned more over the last 10 years about the pleiotropic effects of many of these synthetic molecules that we use in pharmacotherapy, we find that the mechanism of action that we might have

thought of as being singular is actually multifunctional, and therefore these hard-hitting, highly potent molecules don't necessarily isolate their activity to just one gene or just one enzyme, but rather have effects that cut across many different functions in different tissues. That is what gives rise to the potential of adverse side effects over time of use because of this spreading effect of their activity. The natural-source molecules, as I said earlier, which may have lower potency, may hit many things a little rather than a few things a lot and therefore their risk to adverse side effects are often much lower than these synthetically derived molecules. But it doesn't necessarily fit in to our logic from the pharmaceutical world, nor does it fit into the patent structure in that one cannot own a molecule in nature that has already been identified as a natural product.

Many Studies on Natural Products

If we look at things like artemisia (from the *Artemesia annua*) we know that it has a very interesting effect as an anti-malarial. There are many different groups that have been surveying. In fact, 81 clinical trials have looked at anti-malarials from artemisinin, and 31 charities and institutes, universities and companies that have studied it. We also see the role that has been studied in cytomegalo-virus infection (two different studies in that area). We go on to compounds that are derived from triptolide compounds from *Wilfordia* and from Celastrol. These are compounds derived from natural products that have been studied by the National Institutes of Arthritis and looked at for potential activity in autoimmune disease. Again, the mixtures of molecules seem to have a different effect than single molecules. I have been actively involved in published work as it relates to the complex array of molecules found in the lipophilic fractions of hops (the so-called *Humulus lupulus*). These molecules are called tetrahydroisoalpha acids and they also have very dramatic and interesting effects as mixtures of molecules on the kinase-regulated pathways that are associated with inflammatory disorders and arthritis.

We can see that in natural products there exists a variety of very interesting inflammatory modulating substances that work by different mechanisms. Some of them are working by the traditional COX1 and COX2 inhibition activity (that is the cyclooxygenase 1 and 2 inhibitors like the nonsteroidal anti-inflammatory drugs work), and others work by different mechanisms, like the molecules derived as tetrahydrolized alpha acids from *Humulus lupulus*, by modulating the selective kinase signaling pathways that regulate the gene expression of the cassette of genes associated with inflammation that then downregulates the production in inflammatory-prone cells of the synthesis or the production of messenger RNA for the various inflammatory proteins. So it doesn't block the enzyme, but rather it modulates the upstream activity of expression of these proteins in a cell-specific way.

It is a similar situation with capsaisin, which has been used for chronic pain, postoperative pain, radiation-induced mucocitis, alopecia areata, Morton's neuroma, and interstitial cystitis, we have seen clinical trials that have been done in each of those areas. In fact, 13 clinical trials have been published on capsaisin and chronic pain, showing that this hot factor that we find in spicy foods actually has a very interesting effect that modulates the pain receptor and pain signaling mechanism. The paradox is that the hotness that is associated with the capsaisin also retards the heat of pain that is related to inflammation. It is kind of an interesting ying-yang association with capsaisin.

And then, of course, we see some very interesting things with curcumin, coming out the spice turmeric. Many clinical trials that are now being done-there are 6 clinical trials being done on chemoprevention of colon cancer with curcumin; there are 3 clinical trials on pancreatic cancer; Alzheimer's disease, 2 clinical

trials; and chemotherapy-induced mucocitis, multiple myeloma, psoriasis, and cystic fibrosis have all had clinical trials performed with curcumin. It is another interesting molecule, derived from nature, that has influence on signaling pathways associated with cell replication and with metastasis and also with inflammation.[20]

In an earlier issue of *Functional Medicine Update*, we recognized work that is being done on resveratrol, another very interesting molecule derived from peanut skins and grapes. Resveratrol has a very important role in modulating NAD-dependent deacetylases with epigenetic modulation of cellular genetic expression. It seems to control that set of genes that we often call the "longevity genes" that are influencing insulin sensitivity and inflammation, so here's another interesting natural product that is within a mixture of molecules in its natural source. And the list obviously goes on; I'm just hitting the surface. Dr. Mukhtar did a brilliant job of helping us to understand this broad array of molecules and natural sources that have these interesting effects.

If we summarize all this, it leads us to recognize that nature has possibly already been synthesizing molecules with safe and effective activity for the management of certain types of chronic disorders that are not yet severe enough that they require a pharmacological hit. At an earlier stage of a disorder, we are kind of "tickling" metabolic pathways (or the phenome) of the individual (which was the genome, the proteome, and the metabolome)-tickling it with a variety of lower potency but selective molecules that are derived from natural sources, and this may be the both safer and more effective way of managing function over time.

I think this is where the juxtaposition of controversy really exists today--one side against the other, seemingly as if there is no common ground that can be found. I think there is a common ground because it is all about sharing similar concepts of pharmacology. It is all about sharing similar views of this interaction of a biologically active molecule with a cellular function to produce outcome. The controversy is about the orchestration of how that plays out, whether it is an orchestration of a smaller orchestral soloist that is playing very loud and giving a great maestro performance as might be a new-to-nature molecule, or whether it is a full orchestration that is playing together in timber and each voice is attenuated slightly to that of its neighbor to form the complex array of messages that we call the functional web of physiology.

So I think in terms of different molecules for different applications, different thoughts for different needs, and that is where I believe the story really has a commonality of resting between the two sides. It is not that one view is right and the other view is wrong; they really share common attributes of function. It is about using the right thing at the right place and the right time. With the deciphering of the human genome, and looking at how genetic expression occurs and how substances are regulated through the complex kinase signaling pathway (taking outside messages and convert them into inside function)-all of that is leading to a resurrection of interest in natural products, the mixture that comes from substances that have been sieved through this large laboratory process called natural selection. I think that we are going to find that maybe the best molecules of all for chronic management of complaints and restitution of health comes from this laboratory of natural selection.

I hope you have enjoyed Dr. Mukhtar and his comments and I look forward to sharing with you again next month.

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