July 2008 Issue | Devra Lee Davis, PhD, MPH Center on Environmental Oncology

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Welcome to *Functional Medicine Update* for July 2008. I hope you will find this to be very robust and informative issue. We are going to be focusing on aspects of environmental carcinogenesis and nutrient relationships to chemoprevention and how these interrelate to topics we have been exploring this year in *Functional Medicine Update*.

We are very fortunate to have as our clinician/researcher of the month a person whose name is very familiar to many of us and that is Dr. Devra Davis, who is the author of the recent best-selling book, *The Secret History of the War on Cancer*. I think you will find this to be a fascinating interview and discussion with an opinion leader who holds information and knowledge that most of us aspire to understand and know. She can help us get access to that information as we listen to her interview.

I want to remind you that the Synthesis by Jeffrey Bland website is extending and expanding itself. We are doing a blog there, including a video blog to address some of the questions that come up in between each issue of our taping of *Functional Medicine Update*. Sometimes things might be in the news that people are inquiring about. I also give some opinions, and positions, and analysis of various bits of recent published data or clinical studies. You'll find things like this on the www.JeffreyBland.com website. I also want to remind you that we have (through Synthesis) two new home study programs that I think you will find interesting. One is titled *Managing Adrenal and Thyroid Balance Associated with Stress*. You can find more information about it on the website. The second is *The Emerging Therapeutic Target: Improving Therapeutic Outcomes by Treating the Intersection of Osteoporosis, Cardiovascular Disease, Type 2 Diabetes, Arthritis, and Cancer*. If you want to find out more about either of those new products, you can find them on the www.JeffreyBland.com website.

Let's move, if we can, into this month's topic, and that is an extension of our 2008 series on the concept of xenohormesis, the big "X" word. For those of you who are new to this discussion, what this refers to is a relationship. "Xeno" means foreign, and "hormesis" refers to a small amount of something having a larger effect than expected, so "xenohormesis" is a foreign substance having a bigger effect on physiological function than expected.

Xenohormetic substances can either be injurious to physiological function (i.e. distort the web of physiology in such a way as to produce dysfunction that we later call disease) or they could be things that lead to improved homeodynamic balance or improved stability of the web of physiology and increase the resistance to environmental perturbation (i.e. enhance organ reserve). The term "xenohormesis" doesn't

imply a value term as it relates to good or bad. It implies an effect on physiology greater than that which you would anticipate based upon the amount of material. Since "xeno" refers to foreign, meaning coming from the outside environment, this could come from something like a petrochemical polyaromatic hydrocarbon, which would be a xenohormetic response that probably would be injurious to the web of physiology, or it could be a molecule that has come up through natural selection through a diet like flavonoid, an isoflavone, a polyphenol, a proanthocyanidin, that may have a positive impact on improving physiological function or stability of the web of physiology.

There is a very interesting review paper that was just authored by Konrad Howitz and David Sinclair from Harvard University titled "Xenohormesis: Sensing the Chemical Cues of Other Species."[1] This appeared in the journal *Cell* in 2008. The authors talk about the fact that plants make substances of benefit to human health. Actually one-third of the current top twenty drugs in the market are plant-derived and have been modified to make them new to nature so they can be patented, but the ultimate pharmacophore that these drugs were built upon were molecules that were evolved in nature over natural selection processes that gave rise to interaction with human physiology in such a way as to have a xenohormetic effect, meaning modulate complex network physiological function.

Probably the most classic example of a naturally derived drug has to do with Edward Stone testing the bark of the white willow (*Salix alba*) for treating fever; he concluded that it was very efficacious. Today, of course, aspirin is the most common drug of choice in the world at large for the management of many different maladies. It is interesting that the first drug derived from natural products that has now been used commercially for a couple of centuries has really turned out to be one of the most efficacious and probably (when used appropriately) safe. We started off on the right foot, I guess, in appropriating some of these things from nature as it relates to a purified material that was later appropriated into pharmacology as acetylsalicylic acid, which was the chemically modified derivative of the aspirin molecule (or the aspirin pharmacophore) found in the plant. In fact, there are 45,000 metric tons of acetylated derivatives of salicylic acid that are now consumed worldwide each year, which makes it a pretty remarkable compound.

Beyond that, there is this view that these molecules that are found in plants can have direct modulation of key mammalian intercellular signal transduction processes (i.e. the processes by which our physiology is regulated). They are xenohormetic in the way they enhance the body's response to stress. These are molecules like curcumin, from the spice turmeric, or something like the green tea polyphenolic epigallocatechin gallate. In red wines and peanut skins, resveratrol modulates various aspects of cell signaling through kinase modulation (protein kinase C delta or gamma, or phosphotidylinositol 3 kinase, or looking at its effect on SYK or BTK, the Burton tyrosine kinase). We are starting to recognize, at the mechanistic level, how these xenohormetic substances in foods have interfaced and interrelated with the symphonic orchestration of our physiology. The expression of genes into function occurs through interaction with these complex molecules that we eat in a diet with variety and color that are close to the earth (i.e. phytochemicals, by their very nature are derived from plants). It is these minimally processed, plant-derived foods that give rise to these xenohormetic substances.

A number of extraordinary contributors to this field have discussed the evolution of this model on *Functional Medicine Update* over the last few months, and have advanced this whole conceptual framework of how a complex diet and these molecules interface with function. These are secondary metabolites that plants make as their own anti-stress molecules (the flavonoids, the carotenoids, and the

xanthophylls). And these particular molecules then serve the plant to defend itself against environmental stress (insects, sunburn, parasites, infection, etc.). When we consume those plants that contain these complex phytochemicals, they then have influence on our function through these intercellular signal transduction processes in such a way as to modulate our network physiology and to increase stress resistance.

Often we call these antioxidants, but they are much more than antioxidants. "Antioxidants" is kind of a general term that refers to the ability to quench free radical oxidation processes. But well below that, mechanistically, what we are starting to see is that these specific phytochemicals have very distinct and unique abilities, based upon the plant source and the individual shape of the molecules, to influence signal transduction at the mitochondrial level, at the cell cytosolic level, or even at the genomic expression level so that it influences the "trilogy of 'omics" (genomics, proteomics, and metabolomics of the organism) and ultimately its phenomics (how it looks, acts, and feels). Nutrition is being seen to play a much bigger role on physiological function.

By the opposite token, xenohormetic substances that are new to nature (synthetically modulated ingredients in our food like partially hydrogenated, trans-containing fats) have a different role to play on hormesis. Small amounts may have a more dramatic effect on distorting the web and producing alarm reactions-such things as inflammatory modulation in specific tissues. As I mentioned earlier, the term "xenohormesis" doesn't necessarily mean either good or bad influence on physiology. What it means is that each of these molecules, small in amount, may have a bigger effect on regulatory nodes of physiology than we would have anticipated, and it could be a stabilizing influence, or it could be a destabilizing influence.

Decoding the Molecular Origins of Cancer and Examining Chemoprevention

How does this all relate to cancer? That is the main topic of this month's discussion. If you think of the cancer process, as it has emerged to be seen over the last 30 years, it is a process with a series of steps, starting with initiation. Sometimes this is called mutagenesis or the tumor initiation process. Then there are a series of cellular alterations of function that lead to propagation with cell replication and a dedifferentiated state (a juvenile, embryonic-like state), rapidly dividing in a dedifferentiated state. From there it goes into a state of having to feed itself-the process of angiogenesis. Once you get beyond about a three millimeter tumor mass, fixed tumors or solid tumors have to have their own blood supply-the angiogenic process. And then, obviously, the last step, and the most lethal part of cancer, is its tendency to break off certain cells and find sites of infiltration in other tissues. We call this metastasis, and this metastatic process is often the lethal event associated with cancer.

If we look at these particular processes (initiation, propagation, angiogenesis, and metastasis), each one has regulatory-control systems associated with it. One might say that cancer is a complex process of the interaction of the genes with the environment--the whole organism with their environment--that leads to these things that we see clinically (dedifferentiated, proliferative, metastatic cell lines). These cell lines start taking over and alter the energy economy of the host, ultimately creating the potential for a lethal event caused by starvation and by complete alteration of immunological function.

With all of that as a context, how does chemoprevention really work in trying to prevent cancer at various stages (either at the initiation stage, at the propagation stage, at the angiogenic stage, or at the metastatic stage)? Clearly, the earlier that one can engage in prevention, the better off one is. If you can prevent

initiation, you don't have to worry about propagation, angiogenesis, and metastatic events. Obviously there must be regulatory controls at each of those steps in the process. If a tumor is already initiated-a cell is already initiated into a dedifferentiated state (an oncogenic state)-then you want to regulate the propagation (the angiogenic and the metastatic processes) so that that cell type will starve or will be attacked by the immune system in such a way that it will never go to the next stage of development.

Part of this relationship of how tumors get started relates to mutations of the genes as a consequence of injury by a chemical or a radiation event, but also by epigenetic effects (as we have learned earlier in Functional Medicine Update), which mask and silence certain genes, or upregulate the expression of other genes. You would like-in theory-to silence your oncogenes and upregulate the expression of your tumor suppressor genes. It is like a way of putting "bookmarks" on the sections of your book of life that have to do with your oncogenes, saying "Do not read: X-rated." And then you'd like to put "sticky notes" on the sections of your book of life (the chapters in your genes) that are associated with tumor suppressor gene activity and natural killer cell activity, and so forth. You would like this regulatory balance of gene expression at the epigenetic level.

There are "sticky notes" and "paper clips" that are put on, in part, as a consequence of nutritional status. For instance, we know the "paper clips," or the gene silencers, are related in part to methylation of the promoter regions of specific genes. And the methyl groups come by way of what? Through the folate cycle (through s-adenosylmethionine).

Does elevated homocysteine have anything to do with a carcinogenic risk and the increased potential for initiation of a tumor when exposed to a carcinogen? The answer is "yes." Animal studies have demonstrated that undermethylated promoter regions of oncogenes increases carcinogenic risk. That is why folate, B-12, B-6, and betaine become very important nutrients for modulating the gene silencing influence on oncogenes. That is why it is known that animals in a malnourished environment have a higher carcinogen risk (as it relates to pro-carcinogenesis); it is because of the fact that the oncogenes are not as silenced and their promoter regions are available.

So that is one concept. The other concept relates to the activation of your tumor suppressor genes. You want to put the "read here" (sticky notes) on the promoter regions of those genes. One of the groups that causes "read here" are your acetyl groups. Acetylation of the histone and non-histone proteins, as well as the promoter regions, leads to an unfolding of the supercoil structure of the genome so that it can be accessed to read that specific chapter in your book of life. These acetyl groups are put on there as a consequence of available acetyl Co-A. You have to have proper bioenergetics. You have to have the proper Krebs cycle activity (mitochondrial bioenegetics) because if you are malnourished and you have poor mitochondrial function, you are acetyl Co-A deprived and you don't have your acetyl groups available to be put on as "read me" sticky notes onto the histone proteins or onto your genome. We know that butyrate, a very interesting small molecule (short-chain fatty acid molecule), which is produced by gut fermentation of fibers, also has a very important role to play in regulating the "read me" messages on specific regions of your genome are associated with tumor suppression, so we recognize that proper in situ production of butyrate by gut fermentation (by bacteria) of non-digestible fibers (sometimes called prebiotics) is very important as a colon cancer chemopreventive. We have started to understand the mechanism of protection of a fiber-rich meal on colon carcinogenesis.

We are starting to see how these concepts (the initiation, propagation, angiogenesis, and metastatic steps)

actually translate into therapeutic potentials for prevention of cancer. We are really talking here about the molecular origins of cancer. There was a very nice editorial on this in The New England Journal of Medicine in 2008 that talked about how, over the last decade, insights into the origin and behavior of cancers have reshaped our understanding.2 The seminal feature of all this research seems to be the focus on how these steps of initiation, propagation, angiogenesis, and metastasis can be modulated at the cellular level. Maybe the most important thing we have learned since President Nixon stared the "war on cancer" is not necessarily how to treat cancer, but how better to prevent it based upon accessing the appropriate information to prevent initiation, propagation, angiogenesis, and metastasis.

We are also starting to learn that "cancer" obviously is "cancers." It is plural because these mutated cells are different from person to person. We have our own individual cancer that is part of the family of cancers, and so each mutated cell, which may be a mutated kinase or a mutated intercellular signal transduction agent, then plays out its personality slightly differently than other cancers. That is why no two patients are exactly the same when treated, even with the same chemotherapeutic drug or cancer therapy. It is a very, very interesting evolving field. It is almost like studying ecology, with a diversity of species in the environment (when we start talking about cancer, each one having a unique personality).

We are starting to see cancer cell types being genotyped with gene arrays, and then specific types of molecules being used to arrest the mutated kinases in that specific tumor, for example, kinase-inhibiting drugs like Gleevec. It is a different approach toward cancer therapy. But if we back up well before the need for therapy to the chemoprevention stage, we can see that much of what we are starting to understand about the origin of cancer helps us to better understand how to design preventive and early-stage intervention approaches targeted to the initiation and propagation steps.

Endogenous Origins of Cancer

What about things that are endogenous to the human body that might be associated with cancer and its initiation? We think of exogenous substances, like pollutants (and we are going to hear from Dr. Devra Davis today in greater detail about the role that the environment plays in inducing the potential initiation and even propagation of cancer as a consequence of exposure to new foreign molecules), but what about endogenous substances? I am thinking of molecules, as an example, like sex steroid hormones. The one that has probably received the most attention is estrogens and the estrogenic metabolites, which are the hydroxylated estrogens and their quinone byproducts.

As you have heard in the past from an eloquent interview with Dr. Eleanor Rogan from the University of Nebraska, we are now starting to recognize that initiation of cancer can result from endogenous injury caused by chemicals that are present in the normal physiology that undergo chemical transformation. In the case of estrogen, 17beta-estradiol can be hydroxylated to the 4-hydroxy estrogen by cytochrome P4501B1, which then can be oxidized to the 3,4 quinone. This 3,4 quinone derivative of estradiol, as we have learned from Dr. Rogan's work, is extraordinarily electrophilic (meaning it seeks out an electron-dense region of the book of life -- the DNA -- and it chemically reacts with these electron-rich regions in our DNA molecules to produce these covalently-bound, apurinic bases, which then can avoid excision repair mechanisms and induce mutations and potential carcinogenesis). So here is a case where an endogenous molecule, 17beta-estradiol, undergoes an unusual type of physiological transformation process to form the 3,4 quinones. In the absence of proper protection, this transformation can then induce potential carcinogenesis in estrogen-sensitive tissues, which can be the breast, endometrium, ovary, etc.

How does the body protect itself against this biotransformation process, at least to potential endogenous carcinogenesis? Dr. Rogan and the work of other people have identified the fact that there are many steps that can be protective. The body is not just laid naked and exposed to the 3,4 quinones. There is a glutathione conjugation that is possible at the previous step, prior to the intercolation step where you get the reaction of the 3,4 quinone with DNA. So, glutathione protection is important. We know that antioxidation states of the tissue plays a very important role in keeping the semi-quinone from oxidizing into the full 3,4 quinones, so redox potential of the cells, from antioxidants, is important. What types of phytochemicals can find themselves concentrated in tissues where these reactions are ongoing because there are different partition coefficients of different phytochemicals, and there are different transport mechanisms? They don't appear within the same concentrations of all tissues. They have certain tissue affinities, so we might start saying it is not just antioxidants, in general, it is the tissue-specific effects of certain phytochemicals that help modulate the conversion of a semi-quinone into an injurious 3,4 estrogen quinone.
I am going to a higher level of questioning about how we actually develop a science-based chemoprevention program. What would we harness in the way of specific nutrients for the prevention, say, of prostate cancer, or breast cancer, based on what we are learning about these mechanisms? The story I have just talked about with breast cancer and 3,4 quinones of estrogen also applies to prostate cancer in males, where estrogen is also produced in the prostate gland and can undergo oxidation to the 3,4 quinones, as we learned from Dr. Rogan, and can induce initiation of prostate cancer. Here is where sisters and brothers may have similar genes relative to risk, and it plays out in different ways (in gender-specific ways) in the breast in the sister and in the prostate in the brother. These are interesting epidemiological connections. Here is where mechanism and epidemiology tend to converge.

Phytochemicals and Xenohometic Effects Can Reduce Risk
We start asking questions. What are some of the kinds of phytochemicals that have been found to have xenohormetic effects of a positive nature in helping to reduce those events? We talk about things like epigallocatechin gallate in green tea. We talk about limonene, which is a monoterpine from citrus. We talk about curcurmin, but because it is not generally bioavailable, we ask is it the subtle effects curcurmin has on the immunological system that communicates to the breast and prostate? These are still questions that are being asked because we often assume that if there is an epidemiological connection between a phytochemical and a reduced incidence of cancer, the role of that phytochemical must be directly on that tissue. But now we are starting to see that maybe these things can also work indirectly through alterations in specific immunological function. Maybe the functional change occurs at the gastrointestinal mucosa by interaction of flavonoids that are not bioavailable, but influences, at a receptor site in the GI tract, a signaling mechanism that ultimately communicates to tissues at a distance. You'll notice that this is a systems biology approach I am talking about, here, that relates to chemoprevention. It is not so simple as just a single molecule and a single end-point type of analysis.

The mechanism of oncogenic cooperation in cancer initiation is what I have really been speaking to. There is a nice review paper on this whole concept that appeared in the Yale Journal of Biology and Medicine in 2006 that looks at cancer as a disease of extreme heterogeneity, where there are general principles that we can employ to try to prevent this initiation process, or to lower the oncogenic potential, no matter the specific of the gene characteristic of the cancer.3 This is the science-the "new" science, I believe-of nutrition and chemoprevention.

For a simplified version of this whole discussion of cancer initiation and progression, there is a review

paper that I found very intriguing in Theoretical Biology and Medical Modelling in 2006 that talks about cancer initiation and its progression, and really highlights the relationship between the host immune system, their gastrointestinal function, their biotransformational systems and how they can detoxify substances, and their genetic susceptibility or sensitivity based upon epigenetic and genetic loci of sensitivity giving rise to that person's own individual risk to cancer based upon exposure to a substance.4 That is why this field is so complicated because you can't just take an individual molecule and say it has a certain toxicity or a certain carcinogenic potential that is going to be equal in all people who are exposed to it. Cigarette smoking is probably the classic example. We know there are three-pack-per-day smokers who don't get lung cancer, and yet there are people who are exposed to a much smaller level of secondary smoke and do get lung cancer. It has to do, again, with these multiple factors interacting. I'm not even talking, here, about covariables because we don't just get exposed to one thing at a time, we get exposed to all sorts of things simultaneously -- this symphonic orchestration.

With all of that in mind, there is still a unifying mechanism by which we might think about preventing tumor initiation based upon the integrity of our epigenome and our genome and preventing genomic instability. I come back to the wonderful discussion we had with Dr. Michael Fenech about this morphological marker for biological aging and risk to age-related diseases--this genomic instability argument. Ercole Cavilieri and Eleanor Rogan authored a very nice paper titled "A Unifying Mechanism in the Initiation of Cancer and Other Diseases" that appeared in the Annals of New York Academy of Sciences in 2004 in which they talked about the fact that by offering an individual the exposure to the right mosaic of chemopreventive agents it helps to defend against initiating processes that lead to dedifferentiated cell replication that we call oncogenesis.5

The Important Role of Kinases

I think we are starting to witness the emergence of a science base for cancer chemoprevention. You'll notice that I have spoken, at several stages along this discussion, about a class of enzymes that are involved with this intercellular signal transduction process, meaning taking information from outside cells and communicating it to inside cells. These enzymes, whose name you are now fairly familiar with, are called kinases. Kinases are a family of over 500 different enzymes whose role it is to selectively phosphorylate (or put a phosphate group at a specific region on a macromolecule). Kinases are cell regulators in terms of function. There are kinases that work within the genome itself. There are kinases that work by modulating the epigenome. There are kinases that work in the cytosol to modulate, post-translationally, the function of proteins and enzymes. And then there are kinases that work within mitochondria that modulate the bioenergetics of the cell. So these kinases have very important roles to play in transducing signals from the outside world (meaning outside the cell) inside to the regulatory regions of the cell where function ultimately exists.

I've talked about acetylation of the genome that leads to "read me here" type messages. I have talked about methylation that leads to gene silencing, like putting paper clips on certain chapters in your book of life. I also want to make sure you understand that these kinases that phosphorylate various regions of the genome and the histone proteins, ultimately also post-translationally modify active proteins within the cytosol of the cell. These are also very important regulators of the phenotype of the cell (its function).

How does that have anything to do with carcinogenesis and tumor initiation or propagation? The dysregulation of kinases, or the mutation of kinases, has been, in the last 10 years, identified to be very closely associated with the process of cancer initiation and propagation. Regulation of kinase signaling

has a very important role in chemoprevention.

Why am I going into great detail on this? Because the work that we and many others have been doing over the past several years has identified that one of the roles that phytochemicals have in modulating cellular function is their role on specific kinases, and Mother Nature has produced a whole array of natural molecules in these complex diets that we consume that have specificity for modulating specific kinases.

When we are eating foods of variety and a rich array of unprocessed ingredients (phytochemicals), we are eating a complex library of kinase-modulating substances that help to regulate the network of our physiology, the translation of outside messages to inside cellular function. I think that that is an important thing to keep in mind as it relates to how we think about nutrients because often we see studies being done in chemoprevention using one nutrient at a time, where we use a vitamin E or a betacarotene, or a vitamin C, one nutrient at a time, and then we ask, what is its outcome as a drug-like intervention in protection against a certain disease or event? Actually, that is not how the signature of our dietary information influences function in the broader sense. It is not a drug-like effect; it is a systems biology effect by this complex orchestration across families of interrelated kinases that then regulate genomic expression, that regulate intercellular signal transduction, and ultimately even bioenergetics at the mitochondrial level.

This may appear overly technical for you, as you sit there with a patient and ask "What do I do?" The reason I am trying to make this a driving point is that the evidence that has accumulated over the last few years from clinical, animal, and basic science research is that these rich arrays of complex matrices of nutrients appears to have a different effect on physiological outcome than taking one nutrient at a time, or so-called meganutrition, looking at a more pharmacological approach of each nutrient at a time.

Let's use resveratrol as an example as it has been in the news quite a bit. We know that resveratrol is associated with chemoprevention of breast cancer from animal models. Is giving resveratrol at high dose an approach towards chemoprevention that would be justifiable? Obviously that is a pharmacological model. What about lower doses of resveratrol in combination with the multiple other phytochemicals that are found within, say peanut skins, or that are found within grapes, or found within foods that are rich in resveratrol? Does that have a different orchestration of effects when combined as a mixture than when you are using a single molecule in purified dose? It appears, once again, that what is emerging is these signatures of complex mixtures that influence intercellular signal transduction in the cancer initiation process have a different effect. Again, it comes back to eating variety, eating color, and using families of phytochemicals.

Dr. Randy Jirtle, who is at the Department of Radiation and Oncology and the University Program of Genetics and Genomics at Duke University, is one of the fathers of the epigenetics field and has recently published, with his group, a very interesting paper in the Proceedings of the National Academy of Sciences about maternal nutrient supplementation of animals that had been exposed to a known carcinogen (bisphenol A-this is the plasticizer that has been of some concern in plastic bottles as it relates to potential carcinogenesis).6 When these animals are exposed to bisphenol A, it results in carcinogenesis. And when they supplemented these animals with specific nutrients that were involved with silencing oncogenes (that would be your methylating nutrients), they were able to basically show that there was compelling evidence that early developmental exposure to certain nutrients can help to

neutralize the effect of later exposure to these carcinogens, or that early exposure to carcinogens in the absence of proper nutrient intake can imprint the genome to make it more susceptible in later life to carcinogens. It works both ways: poor nutrient intake imprints the genome in such a way as to make it more susceptible over life to cancer; proper nutrition during pregnancy silences the genes and makes the animal less susceptible throughout life to exposure to carcinogens.

Are we doing both things simultaneously in our culture? Are we reducing the level of intake of specific nutrients that are necessary to protect against genetic expression that we associate with cancer while we are also increasing the exposure to carcinogens? This was the theme that Dr. Bruce Ames wrote about in his landmark article and cover discussion in Science magazine many years ago called "Dietary Carcinogens and Anticarcinogens," saying that it seems that we are reducing our anticarcinogenic intake in our diet while we are increasing carcinogenic exposure.7 This construct, I think, is very important Let's say that you initiated a tumor and it started to propagate and needed to undergo angiogenesis in order to feed itself. Are there natural antiangiogenic substances? Of course, the answer is yes. Dr. Judah Folkman, just recently passed away-he was the father of angiogenesis-and what a sad loss that was to the science and medical community. He had been working extraordinary hard over many years in trying to help the world understand the importance of angiogenesis and antiangiogenesis in tumor prevention and tumor treatment. We now recognize that in this angiogenic process of formation of blood supply to feed a tumor, there are many nutrients and phytochemicals that have been found to be antiangiogenic. There is a tremendous amount of work now ongoing as it relates to the role that various phytochemicals have, even after initiation has been established, to prevent angiogenesis and hopefully starve the tumor and make it more susceptible to the body's immune system.

Lastly, let's talk about anti-metastatic agents and the things that are being studied with the hope of being able to prevent metastatic transformation of the tumor (which, as we said earlier, is one of the major concerns that one has in cancer--the metastatic event that leads to seeding in other parts of the body). This is the concept that we heard about from Dr. Hasan Mukhtar who was talking about cancer chemoprevention through dietary phytochemicals. We are starting to witness the emergence of this field, I think, around the major cancers to which nutrients appear to have a very important role--colon cancer, breast cancer, prostate cancer-as being right at the head of the list of those that seem to be very sensitive to nutrient modulation, both at the prevention and maybe even the early stage intervention levels. There are things to consider like Spez PC, the complex array of phytochemicals in Chinese herbs that, years ago, some thought helped in prostate cancer. Through the lens of today, maybe there are things in these complex mixtures that really do influence the processes of initiation, propagation, angiogenesis, and metastasis that frame a new way of approaching chemoprevention from a mechanistic approach.

With that in mind, let's turn it over to our clinician of the month.

INTERVIEW TRANSCRIPT

Clinician of the Month
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Once again we are at that part of Functional Medicine Update that I know you-as well as I-really look forward to, and we won't be disappointed this issue. We have a real treat in store-hearing from someone whose work I have followed for many years and I am very privileged to have the chance to interview her, Dr. Devra Lee Davis.

The name probably even goes without further explanation. She is the author of a recent book, The Secret History of the War on Cancer, and before that the best-selling book When Smoke Ran Like Water. She has a series of extraordinary honors in her background, including being appointed by President Clinton to the Chemical Safety and Hazard Investigation Board. Dr. Davis has a BS in physiological psychology, an MA in sociology from the University of Pittsburgh, and a PhD in Science Studies from the University of Chicago as a Danforth Foundation Graduate Fellow. She has an MPH in epidemiology. She has taken a lot of tests in her life, I can tell that.

Dr. Davis has authored more than 170 publications in books and journals, and her article in Scientific American on carcinogenicity and estrogen relationships was one of the foundations for my thinking. She is a member of the American Colleges of Toxicology and Epidemiology, and a visiting professor at the Department of Environmental Occupational Medicine at Mount Sinai Medical Center in New York. I won't belabor this other than to say that we have a very credentialed and capable person who is going to speak to us on a topic that, for me, started when I first met Rachel Carson many years ago and was very heavily impacted by her book, Silent Spring. Later I interviewed Dr. Sandra Steingraber for Functional Medicine Update, who wrote what I thought was an absolutely fantastic book, Living Downstream.

It is interesting to me that it seems like women scientists are more interested in this topic in men. Dr. Devra Lee Davis is also a female with great scientific credentials in this field. Maybe that's their stewardship of the environment and a sense of mothering the world-I'm not sure-but it seems like the great thinkers in this field are of the female gender.

Dr. Davis, it is really a pleasure to have you here today as an expert on this topic. We started down this road with Nixon's war on cancer, and it doesn't appear as if the outcome of that war was much different than other wars. It just continues on at a level of conflagration, but we have learned quite a bit, it seems (and you pointed this out beautifully in your book), on the area of chemoprevention, maybe more than actual treatment. This history seems to start somewhere back (according to your book) in Germany, with this bifurcation of thinking between the chemical industry and organic food. Can you tell us a little bit about how you got into this and how this all might fit together?

Early Environmental Work Done in Nazi Germany
DD: I was astonished to learn that actually under the Nazis there was a serious program to try to prevent smoking and reduce occupational carcinogens, and at the same time, the site of the world's first organic gardens was at Dachau, where they were making organic honey and trying to encourage young Aryan women not to eat any refined flours and sugars. It was an astonishing thing to learn. It was part of their overall program of racial hygiene, the notion being that they would weed out "defectives" and produce a healthier breed of humans by not allowing German women to smoke or to eat bad food.

JB: And this is at the same time when we saw the development of the chemical dye industry and the start

of what was later to be the pharmaceutical industry. It is kind of an interesting paradox.

DD: It is indeed. Germany was not united in many ways, although one thing that is kind of chilling to realize is that doctors were among the earliest and most ardent supporters of Hitler and of the idea that you could selectively decide who was fit to reproduce, and so they had programs for sterilizing--and later killing--people who they judged to be defective. Of course, among the most defective were the political dissidents, the Jews, the Catholic priests who didn't agree with them-all of them were among those who were judged "unfit" to reproduce.

JB: It is interesting. You point out something that I had never really thought about and that is the origin of the discipline of epidemiology, which allows us to see some of these associations in large population groups between an agent and an outcome. Tell us a little bit about how epidemiology grew out of this soil.

DD: Well, there were some very astute scientists in Germany. In fact, until the early 1930s, Germany had won the most Nobel Prizes and German was considered the language of science. And among the excellent German scientists were people who began to look at patterns in time and space that disease created. They did the first epidemiology showing that tobacco clearly caused lung cancer, but they also observed workers and found that in workers who produced certain synthetic dyes, 100{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of them would develop bladder cancer in 20 years. They had a treasure of information, much of which has been ignored by the West, not just because of its questionable origins, but also because immediately after the war, American and British scientists went over and captured the records and the German scientists who had done this work and gathered that information for the Office of Secret Service (and the British counterpart, as well), but did not share it broadly with the governments or with the workers who were affected.

JB: So there is a longstanding, almost social, history of lack of full disclosure and this concept that maybe it is best that the public doesn't know, "we'll just hold this information in trust," leads to the ability to manipulate, it sounds like.

DD: I think that's right. After all, war crimes are what the losers get charged with. Right after World War II broke out, American companies actually gave the formula to make leaded gasoline to the Germans, the Japanese, and the Italians. Without that formula, they would not have been able to fight against American GIs. And, right after the war ended, Robert Kehoe, the medical director of the Ethyl Corporation, went over to Germany and collected information on what they knew about bladder cancer, and the role of synthetic dyes (diethylsilbestrol), and other things that we now understand were signals of industrial hazard.

Very Early Work Linked Industrial Exposures to Cancer

JB: It seems fascinating to me because I remember studying, back years ago when I took an epidemiology course, that Percival Pott, working with chimney sweeps, had come to the conclusion that testicular cancer had something to do with exposure to coal tar dye in chimneys. It seems like that preceded all of this, and yet it has taken these many years to uncover all of this.

DD: Actually, I was astonished to learn that in 1936, shortly before World War II broke out, the world's leading cancer scientists traveled to Brussels and agreed, at that time, that based on what was then known,

coal tars (like those that lodge in the scrotum) were a cause of cancer (scrotal cancer) in chimney sweeps. They understood that cobalt and uranium mining caused cancer in workers. They knew that x-rays and solar radiation caused cancer, and if you painted hydrocarbons on the skin of animals and gave them solar radiation you could magnify the response. What was considered evidence of cancer in the 1930s was a combination of animal experiments and some human evidence. And what happened after the war was that epidemiology, as a discipline, became interpreted as the requirement before we could say something was causal. The effect of that was to make it necessary to wait until we had enough proof of human harm, in the form of dead or sick workers, or in the case of tobacco, people who clearly had been smoking for a long time. What that meant--because cancer has such a long latency, as you know--is that we were dooming one generation to be experimental subjects in order to decide whether we could try to protect the future generation. That is precisely what we did with tobacco epidemiology, so that not until the 1990s was government action started against tobacco, and when the war on cancer was launched by President Nixon in 1971, it was completely silent about tobacco, although the hazards of tobacco were known in the scientific community in the 1930s and 1940s.

JB: You make such a really remarkable point in your book of helping us to understand the correlation or the association between smoking and lung cancer was brought really from Germany with some of the post-war "intelligencia" that we inherited after the war. It actually became kind of the seed of the anti-smoking research here in the United States, although obviously not heavily embraced by the tobacco industry.

DD: Right.

JB: Who was the gentleman that I think you spoke of that was one of the most charismatic people that carried the banner? That set up the Brunnemann Health Foundation research in Valhalla, NY?

DD: Ernie Wynder was quite an interesting guy. He had been a young man in Germany, and he also was in the Secret Service and went over right after the war to collect information on what the Germans knew. And while he did that, and quite likely learned about their own research on tobacco and lung cancer, he never mentioned it in his own work, and in 1950 with a famous surgeon, he published work showing that people with lung cancer had been smokers. His work, and that of Doll and Hill, appeared in 1950 in the Journal of the American Medical Association.

JB: It burst one of my bubbles when I read about Sir Richard Doll and what I thought were his extraordinary contributions to the birthing of modern epidemiology, and yet it looks like so many of those people were serving also with joint appointments as consultants to the tobacco industry, so some of the work, in terms of the interpretation, wasn't maybe as clean as we might have liked it to be.

DD: You know, it was very saddening for me to find that Richard Doll, who has been a hero of so many of us, had secretly accepted money from the asbestos industry, from the vinyl chloride industry, and from others throughout his career and didn't disclose that funding. So he would publish findings that were quite friendly to the industry, without indicating that they were supporting his work, and we will never really know whether the funding had any influence on the positions that he took. Think about it. If he hadn't cooperated with the asbestos industry, we would not have any data at all on asbestos. That is the challenge for modern epidemiology, as well. We have to have cooperation with industry to get information, and yet because the pendulum has swung so heavily in favor of protecting trade secrets, those trade secrets that a company maintains may have cost my father his life. And it is perfectly legal to

keep information secret, but sometimes what is legal can be immoral. Slavery was legal. Apartheid was legal. But, obviously, today we think those things were immoral. And it was legal for Richard Doll to collect large sums of money from the chemical industry and not disclose it, when he published articles saying that vinyl chloride was not as big a danger as the World Health Organization, itself, had said just a few years earlier. And because it was Richard Doll, a man revered by many of us in public health research, when he reached that conclusion, people accepted it.

Environmental Advocates Face Public Challenges

JB: Going to a more recent time, I know you know even better than I about the vitriol that was written in The New England Journal of Medicine in the review of Living Downstream, Dr. Steingraber's book. And it turned out on disclosure-in fact, I'm very pleased to say that the person who seemed to be the first whistleblower on the fact that the reviewer for her book in The New England Journal of Medicine was the toxicologist for the Grace Chemical Company (that he didn't disclose)-that the first person to point that out was one of my friends, a medical doctor in southern Oregon who wrote a letter to the editor and finally exposed that that had been the case. I think they have said that they have changed their policy now as it relates to disclosure for reviewers. It seems like there is a history, here, of this happening.

DD: Yes, there certainly is. I think that is where our democracy-as imperfect as it is-that is where interview programs like yours play a very valuable function because we are able to get information out. Steingraber's book is a brilliant, brave, bold, and important book. It was very unfairly reviewed in The New England Journal of Medicine by someone who works for the Grace Company, the company that was responsible for massive pollution in an area of Massachusetts called Woburn, where there was so much pollution and so much illness that the people affected actually recovered damages. That's an unusual situation. Most often when people are harmed by toxic materials, it is close to impossible to prove in a court of law what the cause of their harm was and it is becoming more and more difficult to do so. As I discuss in my book, The Secret History of the War on Cancer, the courts have increasingly made it very difficult for people who have been harmed by toxic substances for people to recover at all.

JB: That leads me to your book and you as an author and you as an expert in the field. Obviously you have also engendered the wrath of those who don't want this information to be fully disclosed. Tell us a little bit about your history.

DD: Well, I'm still standing, but there is no question that there have been some unfair hits on my book. One appeared in The New Republic, much to my surprise, where the reviewer actually used material from my book without acknowledging that it had come from my book and accused me of being unscientific when I talked about the role of spiritual matters in helping people to heal and when I talked about my views that complementary and integrative medicine are very powerful tools that we do not fully understand that can often play a remarkable role in helping people recover and do well. When I discussed my friend Les Field, who is an extraordinary, seven-year ovarian cancer survivor (survivor of stage 3-B ovarian cancer), and the work that she did, the efforts of Donna Karan to promote yoga for cancer patients, all of these things, as you know very well, are fundamentally changing the nature of cancer care and the way we think about illness today. This reviewer thought that all of that was just terribly unscientific.

JB: You have known and touched upon in your book a variety of very strong personalities who have also been similarly painted in a certain brush-people like Sam Epstein, who I have had the chance to meet, or Irving Selikoff-what has been your discussion with these people, as colleagues in this area?

DD: We all owe Sam Epstein an enormous debt of gratitude. In 1980 he wrote The Politics of Cancer and the only problem he had was wrong timing. That was at the beginning of what turned out to be the Reagan revolution. Irving Selikoff, of course, really sets the standard for what good, solid research on asbestos dangers should look like and spent years tirelessly gathering records and working with the unions to document the damaging effect of low levels of asbestos and high levels of asbestos on the health of working men and women. I was very grateful that I was able to work with them earlier in my career as well. I think it is fair to say that they both suffered and were targets of attack.

The situation for me now is actually a little bit different because I'm working in a major medical center, the University of Pittsburgh Medical Center. I think the reason why I still have a job is because my boss is Ronald Herberman, and Dr. Herberman is the discoverer of natural killer cells. He wrote one of the 100 Most Influential Scientific Papers of all time. He, himself, has had some unusual personal experiences. He and his brother both developed the same rare cancer of the blood as middle-aged adults. There is no record of this cancer in their family, and yet they had some very interesting exposures. Each of them, as boys, ran in pesticide spray in the fields of southern California, and they became doctors and researchers at a time when young men worked without any protective equipment, and they worked with some known carcinogens. We don't know all of the things that contributed to the fact that both of these brothers, who are several years apart in age, came down with the same relatively rare cancer of the blood, but Dr. Herberman now is the director of the cancer institute where I work, and he has said to me, "Get the science right. We need to have a solid program looking at this." And that is why we have the Center for Environmental Oncology now at the University of Pittsburgh Cancer Institute. We have a website, www.preventingcancernow.org. We have lots of materials available to your listeners about practical things they can do-if they need to treat fleas in their pets, or head lice in their children, there are ways to do this without poisoning them or putting their children at risk-and we have developed all of these materials at a major cancer center because growing numbers of doctors themselves, including my own boss now, understand that we have got to do a better job of reducing our use of things that put us at risk of developing cancer.

Controversial Remarks by Dr. Bruce Ames

JB: That was just so beautifully said, thank you. Once again, that is www.preventingcancernow.org site. We are on the throes of a discussion here that some element of controversy, which makes this very exciting. Let me throw another little wrinkle into the discussion and that is Bruce Ames, who I admire and respect very much as a biochemist, but who has taken a very strong position that carcinogens represent but an insignificant load relative to the overall body burden of potential cancer-producing substances and diet far outweighs the risk as it relates to environmental carcinogens. I know you have a different opinion. I'd like to have you share it with our listeners.

DD: First let me say I share your view that Dr. Ames has done very important scientific work that we are all grateful for. Unfortunately, he has taken a very strong view in areas that he is not an expert in, namely epidemiology, and has suggested that current cancer burdens today are chiefly due to nutrition and smoking and have nothing to do with the environment. His view is wrong, and the reason it is wrong is that we now have evidence from current scientific work that prenatal exposures to very low levels of things like diethylstilbestrol or bisphenol A (a plasticizer) can have profound effects on reproductive capacity, on the health of animals, and ultimately on whether or not they get cancer and the types of cancer that they do get. The most recent evidence of this is work shows that the Agouti mouse, when exposed to bisphenol A prenatally, can develop at twice the size and a different color just if it has had one

small exposure to bisphenol A at a critical period of organogenesis. That is extremely important work. It is parallel to work that was done by McLaughlin and others at the National Institutes of Environmental Health Sciences, where they showed that exposure to diethylstilbestrol, a synthetic estrogen first synthesized, by the way, in the 1930s, early in gestation can cause profound defects in offspring (male and female rats), and that those defects can be passed on to the third generation. And we now see an echo of that in human data generated by the National Cancer Institute that Dr. Ames may not be familiar with. The National Cancer Institute reported just this year that women whose mothers took diethystilbestrol when they were pregnant with them in the first trimester of that pregnancy, have double the risk of breast cancer when they reach age 40. So we now have had 40 years of time for the natural experiments unfortunately to become evident, that children are at risk from things that happened to them before they were born and that it can take 40 or 50 years for those risks to become evident.

JB: This ties together very beautifully with the increasing understanding at the molecular biology/cellular biology level of epigenesis and how modulation of genomic tagging can then express different patterns, say tumor surveillance genes versus oncogenes, and how that can be passed on in the absence of mutations within the genome itself.

DD: I think that is right. We know, for example, that if you look at identical twins and do chromosomal banding analysis, at age 3 they look pretty close to identical (monozygotic, coming from one egg). But by the time they reach age 50, if you look at those same chromosomal bands for methylation patterns, they don't even necessarily look like they are related to one another (if you look at paired twins at age 50 compared to age 3). That is telling us something very simple and powerful: genes give us the gun; the environment pulls the trigger. But the epigenetic effect is really fascinating because that is where I think I'd like to know what you think about the evidence on breast cancer and hormone replacement therapy because some people say the downturn in breast cancer that we are seeing in older women (and it is a slight downturn) is due to the fact that fewer women are using synthetic hormone replacement therapy. If that's true-and I state, if it is true-it is telling us that late-stage effects are working outside of genes (as in, epigenetically) to accelerate cell growth and cause the expression of cancer, or in this case, turning off that cell growth so that even though you stop exposure late in the process, you get a downturn in cancer. But the whole field of nutritional work with cancer is full of examples where nutritional factors seem to be able to turn off cancer processes, even when they are established already.

Xenoestrogens: Collaborative Work with Dr. Leon Bradlow
JB: Yes, and of course you are one of the experts in this field. Again, I had mentioned in my introduction the article that you had authored in Scientific American, and your co-author was the world-renowned steroid chemist Leon Bradlow.8 His work on estrogen metabolism has really created another whole spin on how estrogen might be related to alterations in carcinogenicity.

DD: Indeed. We know, for example, that alcohol is a cause of breast cancer, but most people don't realize that alcohol is highly estrogenic. That is why men who are alcoholics tend to have breasts, and alcohol stimulates the wrong hormone metabolism so that you get a higher amount of 16-alpha-hydroxyestrone relative to 2-hydroxyestrone, and the more 16-alpha (the more "bad" estrogen, if you will), the greater the risk of breast cancer, particularly in postmenopausal women. The question that Dr. Bradlow and I have addressed in some of the work we have done-and, God bless him, he is still doing work today, in his 80s-is whether there are synthetic materials, which we call xenoestrogens, that also can stimulate the production of the "bad" estrogen, 16-alpha hydroxyestrone. We did a study that showed that a certain

number of synthetic organic chemicals including certain organochlorine pesticides clearly increase the amount of 16-alpha hydroxyestrogen.

JB: This is a big presumption, which actually is not a good thing to do, but I'm going go into the unknown here and say if I could try to summarize a platform upon which this discussion rests, it is this concept of how our physiology, from the time of conception (maybe even pre-conception, with the sperm and the egg) is influenced in its ultimate phenotypic expression by the environment through what we might call stress factors, and that could be radiation, infection, chemicals, all these things that you were describing, which really-as you point out in the book-goes back to starting with Walter Cannon with homeostasis, and then Hans Selye with stress, and then more recently Bruce McEwen with allostatic load, so this construct of the environment as a stress factor to physiology seems like a very interesting convergence of thinking of which medicine hasn't really adopted.

DD: I think it is really important. You have been leading a revolution, as I think you know. People are going to look back in five or ten years and say "Remember when we used to give people pills for ills without asking what was in their body and what the status of their nutrition was, their proteins, their enzymatic repair?" We need to be smarter and look at where people live, and where they work, and what source of physiological and psychological stress they are under in order to understand how to help them heal. I think we have generally not done that because the part of scientific medicine that has been carried to extreme is the notion that we can medicalize and use medication to treat most ills. And while we can do a lot of good things with medication, oftentimes medication is masking what the underlying cause of the problem is, as you have written and told people very well.

JB: So if you were to leave a soundbite here at the end of what we could take hours and hours to discuss with your depth of knowledge...if we try to get this into a soundbite, what message might you want to leave with physicians who are listening to this?

DD: The dying words of Pasteur were "Remember the host." Pasteur was the person, of course, credited with the germ theory of disease for understanding smallpox transmission, but as he lay dying, supposedly his last words were "Remember the host." Look at where people work and live, and what they eat and do, and understand that that plays an important role in their health and their illness, and understand, therefore, that the Chinese model of medicine, where we look at the whole person, and we don't simply look at the manifestation of illness, but ask how it evolved, is something we've got to take some good advice from. Looking at the whole conditions that contribute to the health and well-being of people becomes very important. Coming up now, we need to develop better methods for evaluating metal exposure; better methods for understanding historic experiences with nutrition, good and bad; and when we have those tools, we will be more effective in helping people stay well.

JB: That's beautiful. Once again, I want to re-emphasize, on your mandatory reading list, those of you who are listening, should be The Secret History of the War on Cancer. I think that no matter how much you think you know about this topic, you will take the next level of understanding by reading the book and also checking in on the website, www.preventingcancernow.org. I want to thank you, Dr. Davis. You have been very kind in giving us this time. I think you have given a lot of people impetus to take the next step in their education.

DD: Thank you, Dr. Bland. I appreciate your work.

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