October 2000 Issue | James S. Gordon, MD

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Welcome to *Functional Medicine Update* for October 2000. This month we will have a special interview with an Expert of the Month, along with our traditional Clinician of the Month interview. This month's focus is on the role of complementary and alternative medicine in cancer prevention and treatment, and the prospects for regulations on the application of what might be considered complementary and alternative medicine (CAM) products and procedures. We will examine the effect on that domain of passage of the 1994 Dietary Supplement and Health Education Act (DSHEA).

Our special guest, Mr. Loren Israelsen, was the architect of the DSHEA. His draft of that bill, with its many editorial modifications, ultimately was enacted into law. We will get Mr. Israelsen's perspective on the DSHEA, its history, and its future promise.

Loren Israelsen is a lawyer by training, but his activities over the past 20 years have had a much broader impact than. In 1980, he was at Oxford University-Queens College in the Jurisprudence Program. He graduated from Brigham Young University, J. Rueben Clark Law School. Since then, he has been actively involved in the natural products industry. He was president of Nature's Way and has served as a consultant and advisor to nearly every company in the botanical medicine and herbal products areas. He set the standards for regulation of herbs and influenced the government's view of the dietary supplement industry. As a former aide to Senator Orrin Hatch, he has been actively involved in the political process of regulating the natural and nutritional products industry. The DSHEA changed the playing field in the United States in relation to nutritional adjunctive agents and phytomedicines.

JB: Loren, please give us a little history of the events that led up to the passage of the Dietary Supplement and Health Education Act.

LI: It is an intriguing history. In the mid1980s, a confrontation was growing between the FDA and a number of dietary supplement companies, principally in the botanical area. The FDA would use a technique or tool, the food additive provisions of the law, to go after botanicals, such as essential fatty acids, which they didn't like. The problem was almost always with the claims, not with the safety of the product. As you can imagine, this FDA action met great opposition from the supplement industry. FDA and this industry have never enjoyed a warm relationship, I think partially because FDA has never known what to do with products that are neither foods nor drugs but have elements of both.

In 1990 Congress passed the Nutrition Labeling Education Act. This did two things. It created health claims for conventional foods, and it created the nutrition facts box that we now see on virtually all packaged food products. The FDA was required to write regulations to implement that law. In doing so,

they once again dealt what could have been a deathblow to all non-nutrient dietary supplements offered on the market. As a result, I got together with several other people and tried to consider every possible way of solving this problem or series of problems that had grown to life-threatening proportions. We decided the only option was legislation, and from June of 1992 to October of 1994, that's nearly all I did. The DSHEA is regarded by many, certainly by those in Washington who follow legislation, as one of the more remarkable laws enacted in the past century.

A great deal of skirmishing and negotiating took place. The bill, as passed, contains a number of the core provisions we felt were crucial to the survival of the industry. In the waning days of the Congress, the bill went from having virtually no chance of passage, to being railroaded through both the House and the Senate with only hours to go. In the course of those very intense negotiations, literally in the last 72 hours, both sides made a number of concessions.

A Compromise Bill

The law we now see as DSHEA truly is a compromise. It protected and identified dietary supplements as a distinct category of foods. That's the most important principle of the Act. People often don't realize that dietary supplements don't sit alone as a special regulated class; they are foods. This is where a lot of the problems have arisen. Because they are foods, we're governed by food law.

Critics of the bill argue that there aren't adequate safety protections or quality control measures. In fact, that may be a problem. The bigger issue probably is that we have not really finished the job. Among the thousands of dietary ingredients included in the range of items defined by DSHEA, what we do with botanicals, amino acids, essential fatty acids, and essential nutrients? These are very different products and probably ought to be regulated differently, but at the moment, they are not.

The Track Record of DSHEA

JB: What have we learned in the years since passage of the DSHEA?

LI: That's a juicy question! DSHEA passed on a Friday night. I had been in Washington for a long time. Everyone was absolutely exhausted. Our bill was the third-to-last bill passed by the Senate at about 11:30 p.m., before they recessed and adjourned for the year. I remember two things very distinctly. One was thank God it's over. I don't think I could have taken any more. The second was that we had been granted such a sweeping change of policy and of law that I really wasn't sure we were ready to accept the breadth of freedom this bill gave us.

I was particularly concerned about the claims we would begin to see under Section 6, the structure/function claims as they're known. Would those claims be properly substantiated? Would they be the types of claims that were intended by the law? I was also concerned about whether on not quality could be maintained. This law authorized FDA to write good manufacturing practices.

An Unfinished Job

Five-and-a- half years later we are still waiting for regulations on good manufacturing practices. I have to say, I fear there has been an erosion of quality among too many dietary supplements. I also fear too many

claims are being made that are not properly substantiated, or science is being borrowed from other products. Plant extracts are an area of particular concern. A great deal of work has been done in west European tradition a on phytomedicines. Companies have borrowed much of the science on the clinical studies done on one extract and applied them to their own extracts, even though these extracts are different.

I have felt from the very beginning that some inherent problems are there, not to mention simply stealing someone else's data and research. I think the scientific and medical community should be quite concerned about this. Those are my two great concerns.

"Borrowing" Research

JB: I share those concerns with you, Loren. The natural products industry is trying to raise the bar and improve its research base. It can't do that, however, when the equity that some companies have invested is appropriated by others at no expense. Those opportunistic companies then use the research information in their marketing and advertising or reduce the cost of their product to give them a competitive advantage. Will that situation change, do you think, or is it just an inherent idiosyncrasy of DSHEA?

LI: It is an inborn idiosyncrasy of DSHEA. Over the past 12 months, we have seen a significant change in the attitude of the research-based companies. They are tired of being ripped off and are really trying to do something about it. I think these companies will take a more aggressive position toward trade associations and even toward the government. They will ask FDA and FTC to look at the type of evidence being used by some companies, which does not apply between science and product. I think we will see an increased number of watchdog organizations testing products and publishing results.

This is not the way we wanted to see this happen. This ought to be a very thoughtful, self-regulated industry. At the moment, however, we are seeing external forces and people outside the core supplement industry taking the initiative to challenge the quality of products. I think that's been an embarrassment to many. I also feel that's going to turn the tide. We're going to see stronger quality control measures put into place very quickly. Companies are obviously afraid of being embarrassed in front of their retailers and their consumers. That's ultimately what seems to change commercial behavior—the recognition that it's not good business to sell bad products.

The Herbal Products Industry

JB: Herbal products have moved into Wal-Mart and Costco. They have gone from more professional consultative delivery into a general self-help milieu. Mass merchandising has become the watchword, and price has become the driver. Do you think this pendulum will swing back somewhat, or will herbal products remain commodities?

LI: This is probably my greatest concern. Products are regulated under different schemes in different countries, either as over-the-counter medicines or as prescription products. In some cases, traditional medicines have been sold under DSHEA, but as foods. The food business tends to drive on commodity market principles. What we have seen, therefore, probably should not surprise us, but maybe it should disappoint us.

I do think there is a chance we can recover some of the intellectual proprietary assets of some of these products. Here's how I see it happening. Health professionals who initially showed and continue to show great interest in complementary and alternative medicine, phytomedicines, and dietary supplements may have rethought their position. They are afraid they don't understand which products can be relied upon for good quality and good scientific substantiation. They may be advising friends and patients that it may be premature to be actively using these products.

I think we're going to see a push, which I favor personally, to take the very high-end products that are more expensive, because they're backed by research, and grant them a chance to go through the new-drug process at FDA. It may be possible to reopen the OTC monograph process at FDA and allow those products a higher status. This is controversial. Many people feel this would be the beginning of the end of the law of the common, with general and broad access to these types of products.

Confusion among Consumers

However, many people at the moment are saying they really don't know what to buy. They don't know whom to trust. The only solution is that some widely recognized authority, which could either be the government or the U.S. Pharmacopoeia, would say this product has a stamp of authority or a quality seal you can rely on. I believe there's a very strong incentive now to do that. Otherwise, we will remain in the commodity level of business in which the only loyalty in the marketplace is to price. That does not serve anybody well.

These are not inexpensive products to produce. They are more expensive if they are produced to high quality standards and based on research. So I see two or three initiatives happening. I hope we will begin to stretch out the spectrum of claims and authority with which these products can approach the market. That would do a lot to allow health professionals to say they're convinced, satisfied that this is safe, effective, and proper adjunct therapy to whatever they're recommending for my patients.

Concerns of Health Providers

JB: You have had experience as a presenter at conferences for health providers, such as the Columbia University-sponsored conferences on botanical medicine. What has been your experience interacting with health professionals in contrast to those in the natural products industry?

LI: They are very curious about DSHEA. They have heard a lot about it and typically don't understand the law very well. I very frequently give them a quick tutorial on the statute to explain how it's built, why it was done the way it was, and the subsequent regulation, so they will have a framework of understanding. Then, when they read or hear things that are contradictory to it, they will have some confidence that they know what's really going on.

They have two major questions. First, which products in the U.S. market are backed by research, and what are their brand names? That is by far their most important question. Second, how can we tell a quality product from one we should avoid? Are there signs and signals we should be aware of? Those are the core issues.

Physicians' Dilemma

As you can understand, physicians have a responsibility to their patients to give good advice. Unlike an FDA-approved prescription drug, where the quality is assumed to be built into the process and into the finished product, physicians have questions about the process by which these products get to market.

On the other hand, it is a treat to deal with physicians. They really see the value of phytomedicines, essential fatty acids, amino acids, and enzymes, but they're also aware that if a patient has a bad experience with a product they recommend, there are consequences. I hear such earnestness in the voices of these physicians as they want to know how to find out where the science is. How do they know where the quality is? If we can answer these two questions, I really think we will see a second wave and a second renaissance of the natural medicine community when the physicians and the healthcare practitioners will become involved. Until that happens, I'm afraid we are going to remain stuck in an area of ambiguity, at least in the retail sector.

Clinical Applications of Phytomedicines

JB: A number of phytomedicines are now becoming available, from Europe, Asia, and elsewhere. Some specific extracts or formulations have a long history of indigenous use and a fairly significant body of fundamental science associated with them. Do you have an idea which clinical conditions in this country might be most significantly impacted by some of these phytomedicines?

LI: The quality-of-life arena, it seems to me, is really where we will see the greatest initial impact of these products. Only a limited amount of research is being conducted in the European arena, for two reasons. Just as we have seen in the United States, healthcare reimbursement is changing dramatically in Europe. There is tremendous pressure to reduce the price to consumers of pharmaceuticals of all kinds and to become more widely available, by switching from prescription to OTC status. When that happens, companies simply do not spend money on further research. The phytomedicine area has been caught in that pinch.

Quality-of-Life Issues

Second, with the aging population, as we see in all western countries, fundamental issues of quality-of-life are driving the pharmaceutical sector. It's not just phytomedicines. It's true for the most rigorous ethical drug house in this country. Memory, menopause, BPH, and insomnia are basic qualities that mean a lot to people. I think we're going to see some additional research to verify the use of these products for people in this country. One thing that is afoot in this country is studies to confirm European results.

This has happened already on *Ginkgo biloba*. The NIH has funded a very significant study on St. John's Wort, which is underway. They've also funded a large study on *Ginkgo biloba*, which is underway. With the additional $100,000,000 in funding that is going to NIH now, I predict a number of grants will be proposed to do further study in the area of botanicals and phytomedicines. I also expect to see research done in the arena of essential fatty acids, enzymes, and a few other areas.

Medicine of the Future

JB: Looking out a decade, what do you predict will be the domain or environment in which we will operate?

LI: This a very tough question, but I'll take a shot at it. I think we could see two vastly different scenarios. One is that what we refer to now as complementary and alternative medicine will have joined the mainstream, and an important number of products that are today regarded as "alternative" will become very mainstream. The next generation will not even know that at one time there was controversy about whether they should be sold in this country or not. It will be self-evident to everybody that this is part of what we now use for any number of conditions. They will have the full support of insurance companies and healthcare organizations and be widely distributed at all levels of trade, recommended by physicians, sold by pharmacists and perhaps in other locations. It will truly become part of the mainstream. In that scenario, a fair number of products that we see today will continue to be small, niche products driven largely by the range of subcultures in the United States that value certain products, either for social or cultural reasons, that will not enjoy general mainstream acceptance.

A Second Possibility for the Future

The other scenario is that there will be a rejection of alternative medicine, in terms of specific products. That could happen for several reasons. For instance, significant breakthrough drugs that could eradicate major disease areas. I don't think we have any idea what role genomics will play in the next 10 years and how dramatically it is likely to affect health care and our sense of disease and health and wellness. We become fascinated as a country with an extremely high-tech, high-science approaches to health and to medicine. In that scenario, traditional medicines or natural medicines may become passe, and the general public may lose interest in them.

I think something deeply buried in the human psyche wants to believe in a natural approach, or approaches that are more sympathetic to nutrition, to intervention at early stages. I believe that will continue to be true 10 years from now. How it will play out in the regulatory model, I don't have the foggiest idea. I'm not sure anybody who is close to this would have any better luck than I in trying to guess what it would look like. Whatever it is, it's going to be very interesting.

A third option might be that the natural product arena will be viewed as very fertile ground for drug development because of techniques that are so dramatically improved. Hundreds of thousands of plants or other natural substances that have been screened by NIH may have to be tested again because of changes in technology. The sensitivity of methods used 10 or 15 years ago meant we missed all kinds of things that have tremendous value and now we're going to do it all over again.

Contacting Loren Israelsen

JB: Those are fascinating mind teasers. We should check again in 10 years to see where we've ended up. As the founder and the leader of the LDI group, you are actively involved in consulting and information services in this area. I presume that if individuals would like to contact you, they can do so through your email address at LDI at LDIgroup.com. Is that appropriate?

LI: Surely. We would welcome any correspondence. I'm very interested in the views of physicians and healthcare practitioners as to how they see these issues. This is going to be very central to my work in the foreseeable future. Any insights I can gain from your listening audience, I would appreciate.

JB: We'll make sure that we put both your email and business addresses (LDI Group, 1075 Hollywood

Avenue, Salt Lake City, Utah 84105**)** on our summary cards for people to review. Thank you for your years of friendship, your years of extraordinary contribution in making our environment what it is today, and also for your vision and continued vigilance. It's wonderful to know we have people with your mind, spirit, and commitment as part of the team.

It is interesting to see the groundswell or backlash of research information and clinical reports related to the adverse effects of botanical medicines. An increasing amount of published information in various medical and scientific journals seems to be alarming us about the potential adverse effects of these products. One recent report appeared in the *New England Journal of Medicine*, one of the premier medical journals in the world, on the appearance of urothelial carcinoma associated with the use of the Chinese herbs adulterated with *Aristolochia fangchi*. Applications of this Chinese herb include weight loss and improved energy. Not long ago its use in Belgium was reportedly associated with rapidly progressive renal failure in a number of patients who been taking it along with appetite suppressants fenfluramine and diethylpropion, and cascara belladonna extract.

The herbal preparation was found to be potentially nephrotoxic. Its nephrotoxicity was amplified when it was taken jointly with these other products. The active ingredient turned out to be aristolochic acid, which is known to be very nephrotoxic in laboratory animals. An editorial following the initial article in the June 8, 2000 issue of the *NEJM* warns the herb may also have a carcinogenic effect. For more than 20 years it has been known to be a potent carcinogen in laboratory animals. The first case of bladder cancer among Belgian patients was reported in 1994. By 1999, 40 percent of 19 kidney-biopsy specimens from a group of these patients showed multifocal, high-grade, flat, transitional cell carcinoma *in situ.*Therefore, there is a history of danger associated with this particular herbal product.

Aristolochia fangchi, Carcinogenicity, and Nephrotoxicity

One might wonder how the product remains in the United States marketplace, given its history of carcinogenicity and nephrotoxicity. Why is it not regulated? How did it pass beneath the FDA radar screen? Other countries, including Canada, Australia, and Germany have banned the use of this herb. The United Kingdom banned the use of herbs containing aristolochic acid in 1999 on the basis of two cases of renal failure. Yet it is still available in the United States. In fact, Dr. David Kessler, author of the *NEJM* editorial and former commissioner of the FDA, who is now dean of Yale Medical School, said he was able to purchase *Aristolochia* in capsule form very recently in the United States. According to Dr. Kessler, we should not have to wait for harm to occur before doing a systematic safety review. He believes it is time to institute a pre-market safety system.

Others argue the FDA's hands are not as tightly tied as Kessler implies. Dr. Varro Tyler, retired dean of the School of Pharmacy at Purdue University and well-known expert on phytomedicines considers company-sponsored pre-market testing impractical. Manufacturers simply can't afford it, he stated. Instead, he backs a recommendation by a 1997 presidential commission calling for FDA to convene an expert committee to review the wealth of information that already exists on botanicals and then inform consumers and manufacturers about unsafe preparations. According to Dr. Tyler: "No company in its right mind would market preparations deemed unsafe. That would be signing their own death warrant in terms of legal actions."

FDA's Overdue Warnings

Last month, the FDA did distribute warnings to professionals in the supplement industry about the dangers of *Aristolochia.* The action is long overdue, according to Norman Farnsworth, director of the Center for Dietary Supplements Research on Botanicals at the University of Illinois, Chicago. He points out that the dangers of *Aristolochia* are so well known that Germany banned it in 1981 and the World Health Organization issued a warning on the herb in 1982. According to Farnsworth: "If the FDA had been doing its job, they would have banned this stuff 10 to 15 years ago."

How did that product get in under the radar screen? Has the FDA administration simply thrown up its hands? Does it have no sense of commitment to oversight in relation to its responsibility under the DSHEA? Or is it looking the other way for political motivations? The last question is a dangerous thought and sad even to consider. One does wonder, however, with regard to *Aristolochia*, given its long history of nephrotoxicity and carcinogenicity, how it got into the U.S. marketplace and became readily available in various retail outlets.

Forces Creating change

These are types of forces that create sea change. As Loren Israelsen pointed out, these may be the type of backlash issues that ultimately result in a groundswell of interest in changing the law. In fact, I think we can already see the harbinger of change in Dr. Kessler's *NEJM*editorial, as he goes on to say the following:

"It took a tragedy—poisoning caused by the use of elixir of sulfanilamide—to prompt Congress to pass the Food, Drug, and Cosmetic Act of 1938, and it took reports of birth defects among the children of women who took thalidomide during pregnancy to secure passage of the Kefauver-Harris Amendments to that act in 1962. Congress has shown little interest in protecting consumers from the hazards of dietary supplements, let alone from the fraudulent claims that are made, since its members apparently believe that few of these products place people in real danger. Nor does the public understand how potentially dangerous these products can be. Examples like that described by Nortier et al. should persuade Congress to change the law to ensure the safety and efficacy of dietary supplements before more people are harmed."

I think the various visions of the future Loren described are probably going to be promoted by these types of episodes that seem to have occurred as a consequence of lack of regulatory oversight of an industry that now seems to have left the barn door open.

We will be moving from this discussion of herbs, phytomedicines, and nutritional supplements as positive components within the armamentarium of functional medicine therapies, into looking specifically at applications within comprehensive cancer care. Our Clinician of the Month, Dr. James Gordon, will speak to this area. We have asked if there has been a change in the prevalence of cancer over the last several years and if we are seeing cancer rates decrease, We have heard reports that five-year survival rates for cancer have improved significantly. A recent paper in the *Journal of the American Medical Association* questions that statement.

Increased five-year survival for cancer patients is generally believed to mean cancer treatment has improved and that fewer patients are dying of cancer. Increased five-year survival may also reflect changes in diagnosis, however. We may be finding more people with early-stage cancer, including some

who would never have become symptomatic from their cancer. This particular research was done to try to tease apart these two explanations or two potential conclusions regarding the five-year survival rate in the present regime for cancer therapies.

Five-Year Survival Rate and Cancer Mortality

After looking at the data and trying to tease apart those variables, the authors conclude that five-year survival is indeed a valid measure for comparing cancer therapies in a randomized trial. However, analysis shows that changes in five-year survival over time, which have suggested optimistically that we are improving five-year survival, bear little relationship to changes in cancer mortality. Instead, the changes appear primarily to be due to the changing patterns of earlier diagnosis, according to this research.

We are still confronted with the principal question that has plagued us for many decades. What is the best approach toward the prevention and treatment of cancer, given that the modern technologies we have advanced have not been very successful in treating the most prevalent forms of cancer with which we are confronted—cancer of the lung, colon, breast, and prostate.

A New Research Direction

That leads us to question the direction that cancer research is taking. The general theme today in cancer research is on genomics. Researchers are looking at the human genome, identifying marker genes that may be candidates for oncogene mutations that ultimately result in the cell's undergoing de-differentiated replicate of growth. The p53, the *ras* oncogenes are examples. They are looking at the loci within the genome where either mutations or inborn errors encourage the appearance of cancer. Therefore, the focus has been on modulating gene expression, modulating gene risk factors, and finding new therapeutics to manipulate these cell signaling and signal transduction processes. Although these developments are exciting and may bear fruit one day, genomics has not yet resulted in major breakthroughs in improving cancer survival or preventing cancer.

Where Does Cancer Originate? Environment versus Genetic Factors

Where does cancer come from? Is it an inherited condition passed from parent to child, or does it occur as a consequence of uniquenesses in genes that react with environmental considerations and express themselves as malignancy? This is a very polarized question in the areas of cancer research and cancer therapies. Is cancer deterministic or modifiable based upon environment?

Questions like these are the topic of a paper by Dr. Lichtenstein and his colleagues, published in the *New England Journal of Medicine*. The implications of this paper, titled "Environmental and Heritable Factors in the Causation of Cancer. Analyses of Cohorts of Twins from Sweden, Denmark, and Finland," are significant. This study used 44,788 pairs of twins listed in the Swedish, Danish, and Finnish twin registries to assess the risk of cancer at 28 anatomical sites for twins whose twin sibling had cancer.

The researchers used statistical modeling to estimate the relative importance of heritable and environmental factors in causing cancer at 11 of those sites. The purpose of the study, which explored the genetics versus environment issue, was to determine whether the sibling whose twin has cancer is more

likely to develop cancer than a member of the population as a whole.

Environment, Not Inheritance, Is Major Cancer Cause

The conclusion, though not unexpected, is quite remarkable. It was the largest study of its type in twin cohort analysis. The conclusion was that inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. This finding indicates that environment plays the principal role in causing sporadic cancer. The relatively large effect of heritability in cancer at a few sites (such as prostate and colorectal cancer) suggests major gaps in our knowledge of the genetics of cancer. The major forms of cancer, however, are more affected by diet, lifestyle, and environment.

With the exception of uterine cancers, for which no evidence of heritability is found, 20-40{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of cancer was found to be heritable, which implies that 60-80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} is environmentally determined and is potentially modifiable. This model is as profound in changing our view of cancer as was the original acceptance of the fact of the existence of carcinogens that can induce cancer.

For years cancer researchers and therapists did not generally accept that carcinogens, chemicals, or xenobiotic substances had a direct impact on producing cancer. If they acknowledged the effect of these substances at all, they believed their contribution to the cancer process was minor. Now we know cancer initiation and growth are tied to exposure to mutagens and carcinogens. This realization changed our thinking about cancer, moving from inside the body to environmental factors outside the body.

Can we modify our environments to prevent, and possibly treat, cancer? The *American Journal of Clinical Nutrition* contained an interesting review paper titled "Approaches for Chronic Disease Prevention Based on Current Understanding of Underlying Mechanisms." This review describes current evidence suggesting that carcinogens play an important role in cancer production and that we can limit carcinogen exposure. We can do this not only by striving for a cleaner external environmental, but also by pursuing a cleaner food supply system, avoiding moldy grains, aflatoxin-contaminated foods and dairy products, and mutagenic components in broiled meat.

We also know there are agents in our diet, which Dr. Bruce Ames calls "dietary anticarcinogens," that help protect us against mutagenic or carcinogenic injury to our genes. These balances between dietary carcinogens and anti-carcinogens contribute to our risk of the more common forms of cancer, such as postmenopausal breast cancer, colon cancer, and cancers of the prostate, pancreas, ovary, endometrium, lung, and liver. All of these cancers seem to have a strong association with environmental factors of dietary carcinogens and anti-carcinogens.

Chemopreventive Effects of Diet

Fish-eating populations have lower incidence of heart disease and many types of cancers, apparently as a result of increased intake of omega-3 fatty acids. Five to nine servings of fruits and vegetables daily provide antioxidants such as quercetin and isothiocyanates that are important chemoprevention agents. A high fiber intake, including bran and whole grains, is also very important. Polyphenols found in black and green tea are suggested to have protective effects against some cancers.

We are beginning to witness very strong support for the chemopreventive effect of complex dietary principles that may be as important in our understanding of cancer as any chemotherapeutic drug that has been developed over the past 20 or 30 years. We know that whole grains, in contrast to white flour products, contain phytochemicals that are potential anti-mutagenic and anti-carcinogenic agents. A review of this issue, in the *Journal of the American College of Nutrition,* is titled "Mechanisms for the Impact of Whole Grain Foods on Cancer Risk. The author discusses dietary fibers, resistant starch, oligosaccharides, and fermentable carbohydrates that help protect against cancer, as well as antioxidants, phenolic compounds, and trace minerals that boost the immune and cellular repair systems and reduce inflammatory and oxidative stress reactions. This is not just hand waving. Hard science is emerging related to the mechanisms by which these agents participate in cancer chemoprevention.

INTERVIEW TRANSCRIPT

James S. Gordon, MD
Center for Mind-Body Medicine
5225 Connecticut Avenue, NW, Suite 414
Washington, DC 20015
Phone: 202-966-7338
Fax: 202-966-2589
Email: jsgordon@mindspring.com
www.cmbm.org

JB: This month's Clinician of the Month interview features my friend and colleague Dr. James Gordon, who for more than 25 years has been actively involved as a leader in the mind/body medicine milieu. I had the good fortune of meeting Dr. Gordon in the late 1970s. He and I spent a day together during which he showed me around a wing he was overseeing in St. Elizabeth's Psychiatric Hospital where he was Chief of Services. He introduced me to some of the problems encountered with mental illness and how orthomolecular psychiatry and other adjunctive therapies might be of benefit to the patients.

President's Commission on Complementary and Alternative Medicine Policy

Dr. Gordon is a graduate of Harvard Medical School, a chief resident in psychiatry at Albert Einstein College of Medicine. For nearly 30 years he has been a major contributor to the development of mind/body medicine, the force behind comprehensive cancer care conferences in Washington, DC. He recently wrote a book that I highly recommend, titled *Comprehensive Cancer Care—Integrating Alternative, Complementary and Conventional Therapies.* Welcome to *FMU,* Jim, and congratulations on your recent appointment as Chairman of the President's Commission on Complementary and Alternative Medicine Policy. How does it feel to be in the political milieu?

JG: It feels great, actually. I think I've been in the political milieu all my life and certainly ever since I set foot in Washington, DC 30 years ago. I think we have the opportunity, with the Commission, really to move ahead the whole field of medicine. I mean that quite literally.

Our mandate is to look at how complementary and alternative therapies can be integrated into care for

everyone, how research can be more broadly conceptualized, how we can improve the education and training of physicians, other health professionals, and the general public. However, I also see this as an opportunity to bring into the mainstream of medical care the kinds of things we've all been interested in. It's an opportunity to inform all of health care about our perspectives on health care and the techniques we have worked on individually and together over all these years. It's a great opportunity. For me, politics is mostly about how all of us live together and make a life together. It's not so much about the machinations of a few people. If seen in that way, this opportunity is crucial to our health and our health care, as well as to the government.

The Future of Medicine

JB: Jim, your experience spans a significant number of areas. You are not only the President of the Center for Body/Mind Medicine, but also a clinical professor in the Department of Psychiatry and Family Medicine at Georgetown University School of Medicine. You are on the Cancer Advisory Panel for the National Institutes of Health, writing for the cancer conference in Washington, DC. You have been doing this work very effectively for more than 25 years. Can you give us a sense of the evolution of this field and the direction for the future?

JG: That's a big question! The field evolved from a few of us pursuing our own vision and our own understanding in rather different areas, to a movement that is national in scope. It is a very powerful, popular movement and, increasingly, a major movement within all of health care. We've gone from being scattered and, as you and I did in the 1970s, finding each other at occasional conferences, to being a major force. I think we're at a place where we can make a profound difference in how all of medicine is practiced.

We began by informing ourselves and doing our own research on ourselves, our patients, or in the laboratory. I think we've learned enough collectively, so as we put our heads together we can be as important a force in creating a new medicine as the Flexner Report was in creating biomedicine at the start of the 20th century. The kind of work you do and I do, and that we've done together, seems to me to be the medicine of the future.

The medicine of the future is largely about using remedies that can be part of people's lives, not separated from their lives. It is about physicians teaching people how better to care for themselves and about using those things they need to do to survive, like nutrition, breathing, and exercise, at the heart of health care. It is about shifting from a situation in which health care is basically drugs and surgery and everything else is considered ancillary, to a situation in which self-care is central. Those methods that enhance our capacity for self-healing are the next most important and in which drugs and surgery, although eventually valuable, are only used when absolutely necessary. So, I see a real revolution in health care, which we are now in a position to realize.

The Challenge to Complementary/Alternative Medicine

JB: I'd like to play devil's advocate for a minute and ask you to comment on a recent editorial in the *New England Journal Medicine,* which said complementary/alternative medicine has been operating behind the curtains for several years. It has not been subjected to the same level of scrutiny as conventional medicine. It now needs to be put to the test of double-blind, placebo-controlled intervention trials, the

randomized clinical control trials. It will not, according to the author, stand the test once it's subjected to this level of scrutiny.

JG: I agree with first part. Regarding the second part, who knows? It is time we had a level playing field. It is time these therapies were taken seriously, but that wasn't possible until there was money to do it. Many of the therapies we use are non-patentable. Therefore, as you know, no major investment was made in them by pharmaceutical houses or other institutions, until there was real government support or research for the kind of rigorous research that the *New England Journal of Medicine* is talking about. It simply wasn't possible. To damn alternative medicine for something it was not possible to do seems to be a false charge. On the other hand, now is the time to do the research.

The other thing that's really interesting, of course, is that not all of the research is going to be randomized, double-blind, controlled studies. In fact, you may have seen in a recent issue of the *New England Journal of Medicine* the interesting piece saying that there was no evidence that randomized, controlled studies were necessarily any better than case-control studies. I think the challenge is to take a look at these therapies in a rigorous way. Also, let's develop research methodologies that are appropriate for studying them. Now is the time. So, I welcome the *New England Journal of Medicine's* interest in creating a level playing field.

Orthomolecular Psychiatry

JB: In 1968 Dr. Linus Pauling wrote what many of us consider a landmark article in this field. That article, published in *Science* magazine, was titled "Orthomolecular Psychiatry." The term was foreign to most psychiatrists and most people in the mental health field at the time. He talked about the rationale for using higher doses of specific cofactors or nutrients to promote function by overcoming metabolic blocks, using La Chatelier's principles, to get function to occur. As a psychiatrist with many years of experience, what do you think has been the progress of orthomolecular psychiatry or nutritional modulation of psychiatric mental function in those 25 years?

JG: I have to say it has not come very far. I think that psychiatry is way behind some of the other medical specialties in its efforts to be as "scientific" as other specialties. Psychiatry has focused on a very narrow view of biology. I think we've missed the boat.

The talks you gave at St. Elizabeth's were the kind of talks about orthomolecular psychiatry and nutritional approaches generally, that are not being given in psychiatric institutions now, more than 20 years later. Psychiatry needs to play catch-up. Some of the information is there, but psychiatry has gone in the wrong direction, and I'm hoping the new generation of psychiatrists will become much more interested.

The whole field of psychoneuroimmunology should be very important to psychiatry as well, but it has not penetrated as deeply as it should. Psychiatry has suffered in many ways, one of which is that many fewer medical students are going into psychiatry. In 1967, when I graduated from medical school, 10 percent of our class went into psychiatry. Now it is 1 or 2 percent, not only at Harvard, but also at other medical schools. Psychiatry is suffering, and I think it needs an infusion of new perspectives.

Cancer Chemoprevention

JB: Do you feel that cancer chemoprevention is an area in which we have made more progress in terms of alternative and complementary therapies?

JG: Cancer is a life-threatening illness. As a culture we have a fear of cancer. An enormous amount of attention by a variety of researchers has been paid to looking at complementary and alternative cancer therapies. For all of these reasons, cancer is the cutting edge right now. That's why we picked cancer as the focus at the Center for Mind/Body Medicine. The data we have, on nutritional therapies, mind/body therapies, or Chinese herbal therapies are really very striking.

The growing interest on the part of mainstream clinicians in the inventiveness of these therapies is also very striking. We've seen that with the development of our cancer conference. The first couple of years we had 900 people. Last year, we had 1400 people, and three times as many oncologists attended. One thing we've seen is that oncologists in particular, and other physicians, are interested in practical integration of these approaches. That's why some of the information in your book about the effect of food on genes is such an interesting element.

So much of cancer research, of course, is focused on affecting the genes in some way to prevent or treat cancer. Right in front of our noses are these wonderful ways of expressing genetic expression through using foods. This has caught the imagination. It certainly caught my imagination, and it caught the imagination of many of the clinicians that come to the conference. It is an integral part of the book.

The use of Chinese herbal therapies is also very, very interesting, the basic ways Chinese herbal therapies affect biology. Whether it's affecting immune functioning or anti-angiogenesis agents, or having direct anti-cancer effect, I think we're seeing a link between the research that's being done—on mind/body therapies, herbal therapies, and nutritional therapies—at a laboratory level and clinical and epidemiological results. Cancer is providing a wonderful canvas on which we can begin to really paint a picture of the new medicine and how it can be integrated with conventional treatment.

The Role of Integrated Cancer Therapies

JB: Your book, *Comprehensive Cancer Care*, published in 2000 by Harper Collins, contains a number of insights I found very valuable, along with some touchstones going back to experiences I've had along the road the last couple of decades. You have discussed people who have been important along the path—William Fair**,** Ralph Moss, Michael Lerner, Jeanne Richardson. These individuals have a broad perspective on the whole cancer process. They cover everything from the mechanics to the Eastern philosophy to the mind/body interrelationship. Do you see this integrated concept that is evolving as adjunctive or as the central theme, the cancer therapy of the future?

JG: I think it's going to be a central theme. The book is not talking about adjunctive therapies. We are first of all talking about a new approach, actually a more critical approach to all cancer therapies. Part of the goal of the book, and the perspective I think will transform cancer care, is to help clinicians and patients to take a critical look at all therapies and the relevance of a particular therapy, whether it's chemotherapy, radiation, or nutrition, to the particular person.

Assessing the Range of Therapies

Cancer care has been too cut and dried. You have this kind of cancer; this is the conventional therapy. This is what you do; everything else is ancillary. We are saying, wait a minute. Let's take a step back; let's take a look at the whole range of therapies and see how they go together in different ways for different people.

The other thing I think is really important and that will make a difference is that this book is not about some doctor in authority saying I have the answer. This is about creating a healing partnership between physicians and patients, in which together we work out what treatment makes most sense for each person.

Shift in Patient Attitude

The first shift is a shift in attitude of the patient. Once the patient shifts his or her own attitude from simply being a passive recipient or a kind of surreptitious rebel (we know a lot of cancer patients don't tell their oncologists about the complementary and alternative therapies they're doing). Once you shift to a real partnership, then the kind of therapy itself is going to change.

I see nutritional therapies, mind/body therapies, group support, physical exercise and Chinese medicine as being therapies for which there is enough evidence. In the book we suggest that they should be integrated into the care of all cancer patients. Then we see the possibilities from looking at other therapies as, in some cases complementary and in other cases real alternatives to what's offered in conventional cancer care.

Comprehensive Cancer Care

JB: In the analytical, reductionist world in which we live today, we often tend to reduce the whole to its parts, and to assume that by understanding those parts we can understand the whole. People typically read books from the beginning to the end rather than starting in the middle and moving forward or back. There is a sense of linearity, a sense of reductionism in the chapters. I wondered, however, as I read your book if, in fact, one could compare the efficacy of Chapter 3 to that of therapies discussed in Chapters 2 or 5. In other words, is this a whole in which we can separate the parts and get the same thing? Or can we compare one therapy to another to find out what's best?

JG: That is a complicated question! First of all, it is a whole. The human being who has cancer is a whole person. And the particular program each person is going to put together is a whole program. We can also break it up into parts, because at each point you're making a choice about what to include. But when you're finished, it's going to be a whole program.

One mistake we make is in evaluating therapies, because we think people are only doing one particular therapy than we're evaluating. Particularly in the case of an illness like cancer, it's almost never true. Nearly everybody with cancer uses many therapies other than what his or her doctor is prescribing, up to 70 percent, according to one recent study at M.D. Anderson, using complementary or alternative therapies. Almost none of those people tell their doctors about what they are using. The message in the book is that dealing with cancer, having cancer, is best viewed as a journey. Occasionally, it looks linear, but it goes in many different directions, and one grows in many ways on the trip.

Putting Together a Program

The program you put together for yourself at one point in the journey may not be the program you adopt later on. One example in the book is Bill Fair, who was head of urology at Memorial Sloan Kettering, and whom you mentioned earlier. The starting point of his journey was, "I'm just going to take whatever the oncologists have to give me; I've got colon cancer. Just bring on the surgery and the chemo and leave it at that."

But when that particular, kind of linear, approach did not work, he had to open up to all other possibilities because he knew once there was a recurrence, the chemotherapy had nothing to offer. Then he went back with an entirely different question, which I think is the one that opens up linearity and creates holism. He asked, "What can I do?" And it's not only "What can I do—what other therapies are there," but "What can I do?" Once you bring yourself in as an active agent making choices for yourself and creating your own program, then the whole nature of the therapy is different. So it's a kind of back-and-forth, if you will, between linear examination of the efficacy of particular therapies, to the whole individual who is making choices about which therapies to include.

Seeing the Broad Perspective

In the book we try to preserve the spirit of holism and at the same time to focus on the evidence for using, for example, Chinese herbal therapies, with or without chemotherapy and radiation, or the evidence for using mistletoe as an immune-enhancing therapy with or without conventional treatment. I hope we've done it in such a way that people can feel the book fits them and suits them. At the same time, when that part of their mind kicks in that says okay, what are the studies and where can I go to follow up on them, I hope they can also do that. I think both of those functions are part of who we are as people. There is a left brain function and a right brain function.

Breakthrough Areas in Cancer Therapeutics with CAM

JB: That eloquent answer speaks of the web of function and the concept of integration. Cancer patients and practitioners frequently want to know what has been observed that is working. If patients are going to make a decision and perhaps put all their eggs in one basket, they want to have confidence that there have been enough success stories to make it worth the commitment. In your experience, can you give us some insight about where breaks are occurring in cancer therapeutics using CAM?

JG: Yes. First of all, most people don't have to put all their eggs in one basket. They can develop a sound program of nutritional therapies. We drew on your presentation and Dan Nixon's presentations at the Comprehensive Cancer Care Conference. There is a basic nutritional program that everybody can follow, regardless of what they're doing.

There's a basic program of mind/body approaches. There's a program of exercise, one of group support, and one of mobilizing yourself and finding healing partners to help you. Everybody can do these things. I also feel strongly that Chinese medicine—acupuncture, Chinese herbal therapies, and some of the Chinese exercises and meditations—can be integrated into everybody's cancer care. You don't have to put all your eggs in that basket. You can gather a lot of interesting eggs and hold a lot of different baskets as you're doing it.

Looking at What Works

Then comes the situation in which an integrative approach, using those basic therapies and integrating conventional therapies may not work. That's the point where you have to make the kind of decisions I think you're talking about, where you've done this integrative approach. You've done everything conventional medicine has to offer. Or you have looked at the research data on pancreatic cancer and found nothing in conventional medicine promises a cure or a good five-year survival rate. There is nothing even in this comprehensive approach that promises a really good five-year survival rate.

That is the point at which you need to look at therapies that offer radical changes in the way you have to live in order to do them. They may involve your going to another place and committing a great deal of time, money, and energy. In that category, I think Dr. Nick Gonzalez's work using detoxification, pancreatic enzymes, coffee enemas, and a variety of individualized diets to treat advanced cancer, particularly pancreatic cancer, is very exciting.

Programs of Dr. Gonzalez, Dr. Burzynski

We talk about that work in the book. He has presented a series of cases in nutrition and cancer showing that this therapy can not only provide improved quality of life, but that it also can significantly extend life of people with pancreatic cancer. He's now working on a retrospective study of 100 patients with a variety of kinds of advanced cancer in which there is pronounced enhancement, not only in quality of life, but of length of life in these people. That's one therapy that I would look seriously at if I were facing a situation in which there was nothing available for me that really showed a good promise of a five-year cure.

Dr. Burzynski in Texas has also been very much in the news, mostly sort of maligned for his therapies, but occasionally hailed for them. I think that for children with brain cancer, there really is something quite promising there. Again, we talk about his work in the book. There are now 73 clinical trials going of his anti-neoplastins to treat a variety of different types of cancer. I think this is the kind of work we should be looking at and that people need to pay more attention to.

Work has been done on MTH68H, which is a vaccine based on the chicken virus. That work is going on in Hungary and Israel, not yet in the United States. Again, especially with kids with brain cancer, they are getting some very remarkable results. There are a number of therapies.

Then there are other therapies like mistletoe, for example, which is used extensively in Germany and which has anti-cancer effects and immune-enhancing effects. These therapies may have a great deal to contribute. I think each of these has to be looked at and thought through carefully. You have to look at the research evidence, balance what is required for doing the therapy against what you're ready to commit to it and how it's going to affect your whole life, and then make a decision. There's no easy answer in this area, and yet there are certain therapies that are extremely promising.

Objectives for the Next Year

JB: The two research clinicians you just described—Dr. Nicolas Gonzalez and Dr. Stanley Burzynski—were both Clinicians of the Month on FMU. The interview with Dr. Gonzalez was in April 2000, if you want to go back and listen to his comments, and Dr. Burzynski's interview was in February of 1998. What do you see as your major objectives as chairman of the Commission on Complementary and Alternative

Medicine Policy over the next 12 months?

JG: The major objective is to hear from all of you about where you think the field of complementary and alternative medicine should be going. Even more important, how do you feel the complementary and alternative approaches and a more holistic approach should inform every aspect of health care—research, clinical practice, education of health professionals, and public education?

Our goal for the next 12 months is to invite people to come. We want to invite the universe of people who are interested, knowledgeable, and concerned about these approaches to let us know what they think should be happening. What needs to be taught, what needs to be learned? What opportunities need to be opened up? What needs to be changed in terms of financing and coverage so the therapies that are proving effective can be covered?

Town Meeting Series Planned

In the next 12 months we are going to be having a series of meetings here in Washington, about six two-day meetings. We will cover a variety of topics—research, service delivery, public education, and professional education. We are also going to have a number of town meetings around the country where we're going to ask people what their concerns are, what the obstacles are to doing what they feel needs to be done, and what they think the possible solutions are.

What needs to happen, for example, for nutritional therapies to be covered by insurers, or included in Medicare or Medicaid? What kind of education should all physicians have about nutrition? What kind of education should other health professionals have about nutrition? What kinds of education should we have in our public schools? What should kids learn that they're not learning now, and how should it be implemented?

I see my job as opening my arms personally and opening our arms as a Commission, being available for people to put forward solutions. I want to raise the level of dialogue and invite people to help us figure out what kinds of recommendations we should be making to the President, whoever the next President is. Whoever is in the White House definitely will be interested in what we have to say. What kinds of recommendations should we make to people in Congress about future legislation? We welcome all input from everyone who's listening to me now.

Contacting Dr. Gordon

JB: Is there an email or fax number where individuals can send comments or thoughts to you or the Commission?

JG: People can send information to me at jsgordon@mindspring.com, and I will pass it on to the Commission. We can let listeners know as the Commission website and email gets up, exactly what that's going to be so people can be in touch. Anyone who is interested in what we're doing at the Comprehensive Cancer Conference, would like to get the transcripts from the first two conferences, or is interested in our training program can look on our website, which is www.cmbm.org.

An Opportunity for Positive Change

JB: We'll make sure those email addresses appear on the summary cards with this month's tape so people can follow up. Dr. Gordon, thank you. It's been my privilege to be your colleague over the years. I am excited about what the future will bring with you as chairman of the Commission. I think it signals a great opportunity to create positive change in making our healthcare system more humanistic and more successful in improving patient outcomes. I wish you the best. Know that all of our support goes with you and the Commission. I and hope we can make some contributions along the way.

Dr. Gordon brought up many valuable points for our consideration. The *New England Journal of Medicine* recently published a review article titled "Chemoprevention of Colorectal Cancer." The authors discuss the important potential role in preventing the initiation of colon cancer that might be played by antiinflammatories, including aspirin and nonsteroidal antiinflammatory drugs like selective COX-2 antiinflammatories. We are talking about something that ties inflammation together with metastasis and angiogenesis.

The suggestion is that nutrients and phytomedicines are also engaged in promoting antiinflammation. They may participate in ways that are similar to antiinflammatories like aspirin and selective COX-2 inhibitors. These nutrients include products like *Boswellia serata*(the gum resin extract of ancient Ayurvedic herb we know as frankincense) and substances we consider spices, such as ginger and turmeric, which also contain antiinflammatory substances.

Diet and Cancer Prevention

Pharmaceutical and biomedical research is beginning to reveal mechanisms by which some of these processes of cancer initiation can be arrested. Food chemistry and food science technology are beginning to recognize that substances within our complex diet participate in the same way in prevention. Various antioxidants and fiber seem to be protective against colorectal cancer.

The tide is beginning to shift away from an emphasis strictly on a war against cancer toward a symphony in which we are working in concert with the body's immune system and the dietary and environmental anticarcinogens that help defend against the cancer initiation or even metastatic process.

Diet and Recovery after Chemotherapy

Even after chemotherapy, nutrient status needs to be rebalanced for optimal recovery. This situation was the subject of a recent article in the *American Journal of Clinical Nutrition*, titled "Plasma Antioxidant Status after High-Dose Chemotherapy: a Randomized Trial of Parenteral Nutrition in Bone Marrow Transplantation Patients." The authors found that using TPN with the normal levels of antioxidants and minerals found in TPN in patients who had undergone high-dose chemotherapy was not adequate to replete their antioxidant reserves. Plasma glutathione and vitamin E concentrations decreased significantly after chemotherapy. and TPN was not able to replete these levels.

Therefore, there may be need for significant administration of supplementary micronutrients to replete the reserves and to provide proper physiological defense.

Dr. Roy Bean—Blood Test for Cancer Risk—Warfarin for Cancer Prevention

We sometimes learn old things in new ways. I was recently reminded of an interview we did nearly 20 years ago on *Metabolic Update.* (Before it was called *Functional Medicine Update,*this audio magazine was called *Preventive Medicine Update,* and before that it was *Metabolic Update.*) The interview featured we Dr. Roy Bean, an oncologist from the University of Melbourne Repatriation Hospital Medical School in Australia. Dr. Bean had been selectively treating patients with chemotherapy based upon the coagulability of their blood, analogous to Protime.

Dr. Bean found that if he adjusted the dose to minimize coagulability, the patient had a much better prognosis. He had developed a small device that, using microcapillary technology, quickly analyzed coagulation parameters in his patients. He then graded the dose based on their specific parameters from this test. Some interesting evidence, published in the *Lancet* in the 1960s, points to a relationship of ABO blood typing to an individual's response to various first-generation chemotherapeutic drugs. Outcomes and success varied based on blood typing and coagulation parameters after therapy. Dr. Bean had two publications in the 1960s and early 1970s on this coagulation parameter relationship to chemotherapeutic responsiveness.

Coagulation Factor in Cancer

Now, more than 20 years later, the *New England Journal of Medicine* published a paper about warfarin for cancer prevention. This paper discusses the incidence of cancer after prophylaxis against venous thromboembolism by using warfarin. According to this study, a reduction in cancer incidence appears to be a secondary side effect from preventing thromboembolism with this anticoagulant therapy.

Billroth suggested the possibility of such a relationship between the clotting mechanism and the development of metastases as early as 1878, when he described cancer cells within a thrombus and interpreted this finding as evidence of the spread of tumor cells by thromboembolism. More recent indications of a link between the coagulation system and cancer include the thromboplastic activity of circulating tumor cells, the existence of a "cancer coagulative factor," the activation of factor X, and the generation of prothrombinase by tumor cells. These observations have prompted the experimental use of heparin, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs), and warfarin for the prevention and treatment of various tumors in animal models and more recently, in humans.

Diet and Coagulation Factors

Impressive data suggest that aspirin and other NSAIDs reduce the risk of colorectal cancer through the probable suppression of the synthesis of cyclooxygenase-2 and proinflammatory prostaglandins. Only a few published studies of the therapeutic efficacy of anticoagulants against cancer were appropriately designed randomized trials. There is, however, greatly increased interest in coagulation and its relationship to cancer and anticoagulant therapy preventing cancer.

Diet plays a role in coagulation factors. Diets rich in omega-3 fatty acids tend to lower coagulation. Factors related to vitamin E and the tocopherol family tend to prevent platelet adhesion. A variety of flavonoid substances, including quercetin, prevent platelet adhesion. These dietary principles that can participate in these anticoagulant effects may have significant influence on factors related to cancer formation. As I said before, we are learning old things in new ways.

According to the editorial that followed the paper in the *New England Journal of Medicine*,"There is more than adequate evidence to suggest the efficacy of anticoagulants against various tumor types. Certainly, we need more clinical trials, but this does open another chapter of potential importance in cancer chemoprevention."

Moving from cancer chemoprevention to assessing the success of therapies using tumor markers, there is currently quite a bit of interest in appropriate tumor markers for both assessing cancer and following the success of therapies.

"Tumor markers are the biochemical or immunological counterparts of the less differentiated morphology of the tumors. During the past 20 years, there has been a growing appreciation that the morphologic resemblance of cancer cells to embryonic or fetal cells is also reflected in the production of cellular molecules that are more typical of embryonic or fetal cells than of adult tissue. When cancerous cells appear in the adult, they not only look like fetal cells, they also express fetal cell products, which are detected as tumor markers. Many of these macromolecules are not only present in the cell or on the cell surface, but also are secreted into body fluids.

Measuring Oncodevelopmental Markers

Measuring "oncodevelopmental" markers by the clinical laboratory has become increasingly important in the diagnosis of cancer. The first cancer marker, recognized in 1846 by Henry Bence Jones, a London physician, was a heavy precipitate from the urine of a patient who suffered what we now call multiple myeloma. More than 100 years later, Rodney Porter and Gerald Edelman identified Bence Jones proteins as immunoglobulin light chains.

"In 1930, Bernhardt Zondek, a German obstetrician, observed an excess of chorionic gonadotropin (hCG) in some patients with tumors arising from the placenta (chorio-carcinomas), which normally produces hCG. This was the next advance in tumor markers. Since then, a number of tumors of endocrine organs have been diagnosed by excess hormone production. In 1928, before Zondek’s report, W. Hurst Brown of St. Mary’s Hospital in London described the "pluriglandular syndrome" in a patient with oat cell carcinoma of the lung. Pluriglandular syndrome, later renamed Cushing’s syndrome in honor of Sir Harvey Cushing, is caused by excess production of ACTH. Most endocrine organs are linked by common embryonic origin and by the ability of their cells to synthesize and store biogenic amines such as serotonin. These cells are known as the "APUD" system, an acronym that stands for amine, precursor, uptake, and decarboxylase.

The APUD System

"Tumors arising from APUD cells may secrete hormones normally associated with other endocrine glands, and the first indications of tumor development may be the clinical manifestations of that hormone secretion.

"Elevated acid phosphatase in the serum of patients with metastatic carcinoma of the prostate was reported by Alexander and Ethel Gutman of Columbia University in 1938. The percentage of patients with elevated acid phosphatase increases with the stage of the cancer, but the correlation with disease is not close enough to be useful clinically.

"Isoenzymes or isozymes were defined in 1975 by Clem Markert of Johns Hopkins Hospital as different molecular species of enzymes catalyzing the same reaction.

"Van Renssalaer Potter at the McArdle Laboratory in Wisconsin came up with the concept that "oncology is partially blocked ontogeny" in 1969, after noting the similarity of the isozyme patterns of hepatocellular carcinoma to those of fetal liver.

AFP and the Beginning of the Cancer Marker Era

"The modern era of cancer markers began with the discovery of alpha-fetoprotein (AFP) by Garri Abelev at the Gamaleya Institute in the Soviet Union in 1963. Later the same year, Yuri Tatarinov of the 2nd Moscow Medical Institute found AFP in human patients with hepatocellular carcinoma.

"AFP is found in concentrations as high as 10 mg per ml in human fetal serum and in the serum of patients with hepatocellular carcinoma or teratocarcinomas, but in concentrations below 10 ng per ml in normal adult sera. Elevations up to 500 ng per ml occur frequently in association with a variety of nonmalignant diseases such as hepatitis or cirrhosis, but elevations beyond that are essentially diagnostic of an AFP-producing tumor.

"Approximately half of patients with hepatocellular carcinoma may be diagnosed by their AFP level and serial determinations of AFP may be used to determine the effectiveness of therapy.

Carcinoembryonic Antigen

"Carcinoembryonic antigen was discovered by Phil Gold and Samuel Freedman of McGill University in 1965. Gold and Freedman obtained an antiserum that reacted with a protein from human tumors and not from normal tissues.

"In colon cancers and other cancers, the normal polarity of the cells is lost, and CEA is released into the blood instead of into the lumen.

"CEA elevations also occur in association with nonmalignant diseases, so elevated serum CEA can be used only as an adjunct to other diagnostic procedures.

"Prostate-specific antigen (PSA) was discovered in 1979 by T. Ming Chu and his associates at Roswell Park Memorial Institute and was approved for clinical use by the FDA in 1985.

Measuring PSA Levels

"PSA levels are now used to follow men over age 40 for development of prostate cancer. Levels below 4 m g per liter are considered normal."

We are witnessing the emergence of the clinical use of various cancer markers. They include AFP for hepatocellular and germ-cell cancers; CEA for GI, pancreas, lung and breast cancer; hCG for embryonal chorio-carcinoma type cancers; PSA for prostate cancer; and ferritin elevations for liver, lung, breast cancer and leukemia. We are also starting to see tumor markers of cell surface mucopolysaccharoids or

glycoproteins and mucins that may be more clinically definable for certain types of cancer. Thus far no single marker for cancer has yet served the purpose for general discovery.

No Universal Cancer Marker

"The most useful cancer markers at present continue to be monoclonal immunoglobulins, alpha-fetoprotein, prostate-specific antigen, and carcinoembryonic antigen.

"Claims of a universal cancer marker have been made repeatedly but never borne out."

We must be very cautious about using the clinical laboratory in assessing cancer, both in terms of its presence and the success of therapy so that we don't over-read or under-read false negatives or positives from these assessments.

That concludes this month's issue of *FMU*. We look forward to being with you in November.

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