

CHAPTER II: HERBS AND OTHER DIETARY SUPPLEMENTS

Questions & Answers

Q: You mentioned several URLs on the Internet, but outside of the Internet, what would you recommend for consumers and for physicians to become knowledgeable about supplements?

A: There's a publication called the *Natural Medicines Comprehensive Database*, which is just that. It is a very comprehensive and regularly updated document that is probably much more valuable for a health care professional than it is for a consumer. It doesn't mean that the information is not accessible for consumers, but it is probably a little more meaningful for the health professional. The advantage of it is that it's available in a published form and in a Web-based form. The Web-based form is updated daily or as needed. The published version is updated yearly. But it's a very good source of information. There are a number of books that are on the market. There isn't one size fits all. Part of the reason for that is that there are folks who are really very informed about nutritional supplements, and those same people may not be as well informed about the information regarding botanical and herbal supplements. The American Dietetic Association, for example, puts out a book, called *The Health Professional's Guide to Popular Dietary Supplements*, and it's quite a nice reference. I believe it has been updated 3 or 4 times. I think it's better when it comes to the vitamin and mineral and nutrient supplements than it is for herbs and botanicals.

Q: How do you decide what you're going to study? Do you wait until an adverse effect is reported?

A: There are a number of things we consider when prioritizing our research studies. One is potential safety concerns. For example, can we study safety without putting more people in harm's way? There are tools that we can use in order to look at safety and toxicity that don't require human exposure. Use, patterns of use, increasing popularity—

those are the sorts of things we look at. We don't create this list ourselves. I mentioned we use conferences as a way of learning about the state of the art, the state of the science. We try to keep in touch with organizations, both private sector and public, about emerging needs related to dietary supplements. There are so many levels—basic science, as well as the clinical science—that we don't lack for opportunities, and we do have to prioritize.

Q: I've heard that impurities in some of the products may be a significant problem, especially in imported products.

A: Yes. Impurities and contaminants in products raise concerns, and they raise concerns especially if they come from some other countries. I can give you the perfect example. PC-SPES is a so-called Chinese herbal remedy that is derived from a series of Chinese herbs, but it also contains saw palmetto, which is not a traditional Chinese herb. It isn't grown anywhere else except in the U.S. So this is a natural remedy for prostate cancer. Are we getting a message here that this is a product that was being sold for an indication that's probably illegal—disease treatment, disease management? The name ought to give it away. PC-SPES—PC for prostate cancer, and SPES the Latin word for hope. So there was a marketing influence here. Now why am I even bothering to tell you that? Because there was a potentially very valuable tool in the toolbox for the management of people with estrogen-insensitive prostate cancer. It shouldn't have been a dietary supplement. Don't get me wrong. This was a product that held some promise, and the NIH—NCCAM primarily—embarked on a series of clinical studies related to this until the product was found to be contaminated. Sadly, different batches of the product were not contaminated with the same thing. Some of them were contaminated with diethylstilbestrol, which might explain some of the ameliorating effect that some versions of the product had—it doesn't mean that it did, but it might have. Others were contaminated with other things, and it may not have been deliberate. It might have been, but I honestly don't know that. But the fact is that the herbal extracts were brought into the U.S., and they were presumably already contaminated at that point. So there's an example, and we do have concerns about this. Indeed, so does the FDA and so do manufacturers. They're

concerned that the reputation of the industry as a whole is being sullied by the actions or inactions, areas of omission or commission by some companies that don't adhere to the same rules. The FDA is about to release something called *Current Good Manufacturing Practices*, which is a set of guidelines, a set of rules, by which companies must adhere if they're going to put products on the market. You say to yourself, "Why weren't these there in the first place?" It took a long time to get them out and cleared. But this, we hope, will be a way of dealing with the issue of contamination, as well as just the general issue of quality of products in the marketplace. But contamination is, no question, one of the things that needs to be dealt with.

Q: This brings up an issue that Dr. Straus mentioned about dietary supplements, when he was talking about looking at labels on supplements, that they're not actually accurate. You don't really know what you're getting. You're saying that we should read the labels, but that doesn't always work because there are other contaminants.

A: It has to do with what appears to have been a discrepancy between what I said and what Dr. Straus said last week. Actually, I don't think it was, but let me see if I can't clarify it for you. What Dr. Straus was referring to, and I enthusiastically endorse this, is that products are not obliged to come to market with proof that what's in the bottle is what's on the label. The label can say something, but it is no guarantee that that's what's in the bottle. I showed you a label before from a company that markets Centrum. Centrum, I would think, is a very high-end product manufacturer. They would likely not be willing to put a product in the marketplace that was harmful or was garbage because it could compromise the sale of a whole line of other things that they sell. They're more likely to adhere to good manufacturing practices, which in turn would mean that with their quality standards by which the products are manufactured, that they're much more likely to have what they say they have in them because testing has actually been done during the course of manufacturing it. The key thing is that that's not been required, and eventually, when good manufacturing practices are put into place, it will be required. Companies that can adhere to those will remain in the marketplace, and companies that

can't, won't. That may deal with some of the issues, not just in terms of contamination but also in terms of quantity of actual ingredients in the bottle.

Q: Will those regulations affect foreign companies?

A: Anybody who wants to market a product in the dietary supplement category in the U.S. will be regulated the same way, foreign or not. It turns out that most of the companies doing business in the U.S. are American companies. They may be American arms, in some cases, of companies that have homes abroad. But many of the products that are marketed in the U.S. are bought in bulk by American importers, suppliers, or manufacturers, and they are actually often bought from the same sources and then they may be made to different specifications once they're here. But you're absolutely right to be concerned, and I think also to be reassured that the regulatory arms of the government and their partners—the industry—have an active partnership. Nobody wants the circumstance to occur in which a product is brought in that could be a vehicle for a transmissible disease. I can't say for sure that there is no risk. I would never do that, but it was of sufficient concern both to the FDA and to the trade associations that represent the supplement industry to have engaged in very active discussion about this and want to make sure that nobody feels as though importing allows them to get around the regulations.

Q: Does the dietary supplement industry do any significant amount of safety research, and if so, do they follow NIH guidelines?

A: The answer is not very often in both cases. There's an explanation for why companies do very little research, in fact, of any kind with respect to dietary supplement ingredients. What it comes down to is that there is no return on investment for them. Dietary supplements are essentially generic. If you think of generic drugs as being knock-offs of prescription drugs/branded drugs, essentially all dietary supplements are generic. Although your St. John's wort might be different from the St. John's wort that somebody else makes, it might be made to better standards. It might have more active ingredient in

it than somebody else's, but you're not going to get much credit for that because it's a generic marketplace. If you want to patent your process or if you want to market it as a botanical drug, you can do that, and you might get around some of these concerns. But the fact is that there's little incentive for companies to do that. The law is based on the fact that supplements are like foods. They're safe until proven otherwise. If you think about that, it means that there's a whole lot that's already taken for granted. I personally think you shouldn't take that for granted, and I believe that more and more people, certainly in my area of science, as well as in the responsible ends of industry, take that seriously as well. But frankly, research is expensive, and dietary supplements can go to market without having to do much research. So given that, who's going to do the research? It's much more likely that the NIH or some other Federal agency will embark on or lead, in a partnership perhaps, the scientific charge.

Q: I was wondering if you have any research or plans to do any research on metabolic compounds to lower cholesterol levels in lieu of statin drugs.

A: There is a fairly active ongoing research portfolio in that area. It's complicated by the fact that the most active component of some of the most effective statins from plant source—Chinese red yeast rice, not a plant, is actually the major source—is exactly the same compound that is in Lovastatin, or Mevacor, the drug that started this whole revolution of statin drugs for cholesterol-lowering. It has created a war between the drug companies and the supplement companies about whether or not supplement companies are marketing an illegal drug. There is this tension that always goes on in this area, but yes, it's quite a promising area. Just as an aside, one of the most appealing things to me about that field is that in Chinese red yeast rice, at least what I've seen so far, there is a mixture of compounds that have sort of synergistic effects on plasma cholesterol level. The total amount of statin that you require from that source is lower than you would require from the purified mevacor in order to achieve a comparable effect. Now there are promising data that point to that. It clearly needs to be much more fully elucidated when the lawsuits are done.

Q: Based on what you said about variation in content of supplements, for the over-the-counter vitamins, the multivitamins that people take every day, how close is the label to what they're actually getting?

A: Even for vitamins and minerals, the question about product quality needs to be asked. Ironically, it's not done in a premarket kind of way because as I told you, companies are not obliged to provide that kind of information before they put a product on the market, at least not until now. Therefore, the only way that people know this is by somebody going to a supermarket and buying 10 versions of a multivitamin made by 10 different companies and measuring the content. This is true of all supplements. Some do very well. Some come pretty close to the label amount. Some don't have anything in them worth noting, and some have more than the label implies. Now that problem, generically, is true about supplements. It's not so true for vitamins and minerals. There are a number of reasons for that. These are pure compounds for which methods of measurement and analysis are readily available and have been used for a long period of time. More often than not, these are made by companies or they're marketed by companies that are usually getting their material from a lot of the same places. The quality control is better for vitamins and minerals than it is for botanicals. But the problem is there sometimes. One of the companies that does this sort of postmarket testing is called ConsumerLab.com. You can go to their Web site to get a sense of what they're doing in this area. It's taken companies like that to actually get people's attention because there's no premarket requirement for this information. Where do you go? Postmarket and then get it that way.

Q: On the Centrum label you showed before, does standardization have any meaning?

A: What's the meaning of the term standardized when it relates to extracts like this? It's a little in the eye of the beholder. What I would like it to mean is that if I buy Centrum St. John's wort today and then my son goes and buys it in another store in Philadelphia 2 weeks later that it's going to have the same thing in it that mine did. That's what I would do so that quality is controlled. Now the problem is with the word standardized. It also implies that you know exactly what's in it, and you don't. Even for something like St.

John's wort, it's standardized to something that is almost certainly not the active ingredient. So what then does standardized mean? It does mean that it's made so that each batch has about 0.3% hypericum in each batch, but hypericum is not the active ingredient, so do you care? Yes if hypericum is a good marker for the process of quality control. But it's a reminder that this is a bit in the mind of the beholder. But I'd like to think that by standardizing you get to a more reliable version of the product from time to time.

Q: Are American medical schools including this in their curriculum and are we doing anything to encourage that?

A: The answer is very little, but then there is also very little nutrition in the medical school curriculum. That process is improving a little bit with NIH help. I'm rather hopeful that we can sort of follow in those footsteps. If we can't do it for nutrition then it's hard to imagine being able to do it for dietary supplements. In this respect, we will follow very closely how our nutrition colleagues evolve their tools for getting us into the curriculum. We will certainly expect to be part of that. It's hard though. In schools, what academic course would you like to give up so that your kids can have gym? There's just so little time available in a medical school curriculum. I don't think that's a good reason for not including this terribly important information, and I think physicians probably need to know a lot more than they do now.

Q: Will the focus on safety deny people access to a worthy intervention? What are your supplement recommendations?

A: I used PC-SPES as the example of where contamination created problems, and you're expressing the appropriate concern that our focus on the safety might deny people access to an otherwise worthy intervention. That is a tension that we struggle with. In fact, when I said that this product showed promise, I would have preferred to see it developed through a proper drug development route to demonstrate its efficacy, to look at its safety profile. Are all 9 of those herbs necessary in order to achieve the effect? Nobody

bothered to look at that kind of stuff. In my view, that meant that the American consumer, the patient who is relying on this, is really being done a disservice. I am hopeful that the product can be reconstituted, re-evaluated in a proper way, and brought back to the market as what it should have been in the first place, which is a drug. We are always worried about that kind of thing. I don't want to be in the situation where I'm being told I'm denying Americans access to worthy products, but frankly, the information about some of them would give you pause to question it too. Now in terms of recommendations, I don't generally make them. I happen to take a multivitamin, and if you were to ask me, "On what basis, Dr. Coates, do you take a multivitamin every morning?" I'd have to say that "the information is a little bit here and a little bit there." There are some things for which the evidence is firm. For some things, the belief system is high, but the chance of doing any harm is virtually nil because I do read the label when I can see it, and I am aware, especially when my wife reminds me, that there is a concern about men in their 50s ingesting too much iron. So I'm aware of that sort of thing, and I don't take it lightly. I make the assumption that even a multivitamin is the same—it's a medication as far as I'm concerned. That is a very personal bias. It's how I would approach this. I make the assumption that anything you ingest you need to be thoughtful about. There are some things that are really good for people at various times in their lives, and it may be that, for example, supplemental calcium is good for everybody all the time. I honestly don't know that, but I am acutely aware of the fact that teenage girls and young women take in less calcium than they probably can afford to in order to support bone health. So the recommendation to take calcium early in the life of a young woman is a good recommendation. They are very likely to continue to take it, by the way. Folate for older individuals is probably a very good thing to take. The best way to take a vitamin is as a supplement because it is not very well absorbed from foods. So there are examples, but sometimes they're specific to the population in which the studies were done and cannot always be generalized to everybody.

Q: Herbal teas widely use caffeine in their tea. With herbal teas, should we be concerned about any of the problems that you raised about herbal supplements generally?

Considering the general statements about health that the dietary supplements make, do we have any information on that with herbal teas?

A: Not really, but I think you can take some comfort in the fact that herbal teas do have a history of use as teas, unlike capsules containing catechins or lutein or something like that. There's less information, less basis for study of them in that form. But teas generally have been used as part of cultures for millennia. So I'm less likely to be concerned about them or their contents unless they're made or concentrated in any particularly unique ways. If they're used according to standards that have been practiced for a long time, it's unlikely—I never say never, but it's unlikely—that there would be harm.

Q: Are there any certifying organizations?

A: The U.S. Pharmacopeia, or USP, designation on the label comes from the pharmaceutical sort of culture where standardized products—products made according to certain kinds of standards—can have their process approved or certified. The USP is one of those certifying organizations. They also certify dietary supplements. You've seen this on labels, so vitamin D may well have the USP designation on it, which would certify that it's been made according to standards that are accepted by that organization. There are a couple of other organizations that do that as well. It is a measure of quality. It says nothing at all about efficacy or safety, just so that we're clear on what it does offer and what it doesn't offer.

Q: What is your research budget? Do you do joint projects with outside groups?

A: We receive an appropriation from Congress, as does every other organization within the NIH, just for your information. It's a little under \$20 million this year so it's relatively small. What it means is that we actually do have to partner a lot. We mostly partner with our other Federal colleagues—organizations like the National Center for Complementary and Alternative Medicine. They've got a bigger budget than we do. We note that. The National Cancer Institute has a huge budget. We note that—2, 3, 4 times.

So we do partner with these organizations in order to move the research agenda forward. In some cases, it has meant partnering with organizations outside the Federal government as well. This is a practice that has been used a lot in terms of trying to move research agendas forward.