October 2015 Issue | Robert Rountree, MD

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Welcome to *Functional Medicine Update* for October 2015. Oh, what a treat we have now in our third installment of our four-part series on the gut microbiome, and that is with our long-term champion and key opinion leader Dr. Robert Rountree, who was with us as an FMU Clinician of the Month a number of years ago talking about pediatric nutrition and immune health. With that as an introduction let's move directly to our fascinating discussion about the ecology of the gut microbiome with Dr. Rountree.

INTERVIEW TRANSCRIPT

Clinician of the Month

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So once again here we are with one of the world's leading experts in the clinical application of these concepts that we've been describing over the past few issues. That's Dr. Robert Rountree. You know Bob is one of our seminal leaders in the functional medicine field, and an individual who graduated Magna Cum Laude from the University of North Carolina in Greensboro in 1976 and received his medical degree from the North Carolina School of Medicine in Chapel Hill in 1980. He did his residency in family community medicine at the Urgent Medical Center in Pennsylvania, and he is certified by the American Board of Family Practice.

He has been practicing family medicine, utilizing really a comprehensive approach that integrates much of the functional medicine parameters since 1983. I've had the privilege of knowing Bob from the early 80s on, so he and I have shared a journey through this evolution of healthcare over those last three-plus decades, so it's really a great treat to have not only an expert, but a person who has been a thought leader, authoring chapters in the Textbook of Functional Medicine, Clinical Botanical Medicine, and Clinical Natural Medicine Handbook. The New Breastfeeding Diet Plan was one of his books, and also Immunotics, talking about nutrition and immunology, and Smart Medicine for a Healthier Child. So you

can see just from those titles that Bob's range of interest goes from preconception all the way through the aging process and its application of good medicine. He is one of those individuals who takes very complex information and can bring it down to the level of understandability to the average both clinician and patient.

An Ecological Approach to the Microbiome

I thought that we could entertain Bob with a discussion theme in this particular issue of Functional Medicine Update around an ecological approach to treating disturbances of the microbiome. And the reason I chose ecological is that Bob is really the master of integration of the big to the small, of the global to the individual. Ecology cuts through all of those. Ecology comes from the Greek word that means "home," and so we can be at home in our bodies, we can be at home in our world, and we can be home in our universe, and Bob has done a really good job of integrating all of those.

Welcome, Dr. Rountree, to Functional Medicine Update and thanks so much for being available.

RR: You bet, Jeff. It's great to be back again.

JB: So let's start with an outlining perspective question. You are the 2015 Institute for Functional Medicine Linus Pauling Award recipient, which is the top award that the Institute gives to individuals of distinction. So maybe you could tell us briefly about your path that led you to the point in your career and the origin of your environmental advocacy in medicine, which highlights much of what you have been able to be as a leader.

RR: Well, it really started for me as a small boy growing up in a very rural area in South Alabama, believe it or not. My family owned an area outside of Montgomery, Alabama that was actually used part time as a Girl Scout camp, and that's where I spent my early years. It was really swampy and very, very biodiverse, and so the early years of my life I spent going out and exploring the woods and was really fascinated with the mixture of wild animals—all the reptiles, in particular, and the rich sounds at night of the frogs and all the insects chirping. I thought that was the way the world was. I think that kind of set the theme for me. As I got older I spent a lot of time camping in the woods and summer camp was always something that I greatly looked forward to, and then when I got older I got into backpacking, and then later sea kayaking which is one of my all-time great loves. So I think that has created this ongoing theme in my life—an appreciation for what nature has to offer.

When I went to medical school it was partly because of an inspiration I had studying biology. I still remember looking under a stereo microscope for the first time and watching cells divide, and I just thought that was the most amazing thing in the world. I imagine when Leeuwenhoek first was able to get that famous drop of water and look at it under the microscope and realize it was full of all these living things how mind-boggling that must have been. I would say I shared a similar kind of inspiration. So in the back of my mind it has always been about the biology and the systems (the biological systems) out there that has inspired me. That's really what's moved me forward through all this.

JB: So taking that as a really great frame of reference and then projecting it forward into your professional life as a medical doctor, you've obviously become recognized as a thought leader in the area of human ecology, which connects the external world to the internal world. How do you think this

expertise and this perspective influences how you see a patient and the questions you might ask or the communication you have with a patient? It would probably be interesting for individuals to know how that framed some of the interrogation that you have with your patients.

Applying Chaos Theory to Perturbations in the Human Body

RR: Well, I guess I'm always looking at things on many different levels. In medical school, you're basically taught the one-disease/one-treatment model, which is very linear, very narrow-focused. But I'm always pulling back with my lens to say, what is the big picture here? When I first started giving lectures for IFM, I put a big emphasis on chaos theory. And part of the reason I was so fascinated by that was the idea that any small change—any small perturbation—in the initial system can lead to huge ramifications. The whole idea that a butterfly flaps its wings in Texas and that sets off a tornado in Brazil. If you think about that in the gut, which gets to our subject of the microbiome, then it has fairly profound implications—that you can have one change in a keystone species of bacteria, or a virus, or a fungus that can have a rippling effect on the whole body. I often talk with patients about this, how small little changes can have huge effects on their overall health. And again, that's very different than using a blunt tool like a pharmaceutical to try to come in and block an enzyme system and cure an illness.

JB: Yes, I think that's a beautiful segue into the gut microbiome focus of this issue. We know that the outside and the inside worlds connect at the gut microbiome level. This seems like something that those of us who have been in this field for some years might find very sensible, but for the average patient that might be considered quite an unusual concept because first of all they're not even familiar with the fact that they've got nearly two to three pounds of living critters in their intestines, which is the microbiome that is responding to the world. How do you communicate this concept to your patients—this kind of gut-communication microbiome story?

Introducing Patients to the Microbiome

RR: I kind of start with this notion of how far we've come since we developed this DNA probe technology. I attribute that to people like Rob Knight who is right here in my town at the University of Colorado. Once they developed that technology to fairly rapidly identify what's out there, one of the first realizations was that we are basically covered in microbes, that there are no sterile compartments in the body. That, I think, was a huge development. You know, we have gone from a place in microbiology of being focused on pathogens and thinking well, there's a handful of bad bugs out there and if you are unlucky enough to get exposed to one of them, and if you're unlucky enough to get some salmonella in the food that you're eating, then you can develop a pretty bad gastroenteritis, and so that gets us back to the old Howard Hughes notion that we'll just sterilize all of our surfaces and we're not going to have to worry about all these bugs. So it has actually created a bit of a paranoia about microbes and what's out there because we tend to think that most of them are bad, and what Dr. Knight has done, what Jeffrey Gordon has done in St. Louis, and Peter Turnbaugh who was at Harvard, have basically shown that we're swimming in a sea of microbes, and those microbes provide—what they say in an ecological perspective—is ecosystems services.[1] You know? In the same way that a salt marsh provides an ecosystem service.

So these microbes are doing good things for us, by and large, and we're swimming in a sea of them, so the first thing is to start thinking of them as our friends: Some of my best friends are microbes. If we can

change people's attitudes toward microbes and stop thinking, well, you've got to sterilize everything, you've got to be paranoid, you've got to be careful, you've got to nuke all you food so that you don't, God forbid, get exposed to bad things, then it's going to change your whole relationship to microbes and that is especially true for the gut, for the nose, for the lungs, realizing that most of these microbes are acting in a friendly way and that we really need them—we desperately need them. So we need to think about lifestyle practices that will engender the growth of healthier microbes. And it's not just healthier microbes, it is microbes that exhibit healthy behavior.

JB: Yes, I think that you've really done a beautiful job of describing this concept. This seems like almost back to the future that we are revisiting the importance of this microbial world that we live hopefully in harmony with. It also reminds me that this microbiome that you're describing is more than just in the gut. I'm recalling the work that is being done now on COPD and the microbe of the lung and how that's interconnected somehow with the speciation of the overall body's microbiome, and so if you have a disturbed microbiome it actually changes your cardiopulmonary functions. It's really powerful reframing of this whole conceptualization of living in harmony.

Maternal Microbes and the Birthing Process

RR: Well this whole notion that there really is no sterile surface in the body I think is pretty profound. I recently was reading through Rob Knight's book Follow Your Gut.[2] It was published by TED Books. It's a nice book because it's short and sweet and really gets into the point. And he has some very pithy statements that are, I think, quite profound. One of them is: "Vaginal microbes determine our destiny."

JB: Oh, that's right because of the birth canal, and in fact when we talked with Dr. Blaser he spent quite a bit of time talking to us about some of the adverse implications of using antibiotics during pregnancy and the birthing process and also about the rising prevalence of C-sections and the lack of having exposure to the vaginal microbial environment.

RR: Well we know that those vaginal microbes basically set the tone for what our entire microbiome is going to be—not just the gut microbiome but what's happening all over our bodies. That critical time of birth is going to have an influence on the rest of the person's life. And it brings up its own issue that is a very thorny one of almost mandatory screening for Group B strep in pregnant women and then giving them antibiotics even if they have no symptoms or risk factors for neonatal sepsis. It's a really challenging issue because there's not a clear answer, and if you are able to show that you prevent neonatal sepsis by giving antibiotics shouldn't that be a good thing? Well maybe, but what if that also means that child is also more likely to develop inflammatory bowel disease later in life? That's a bad pay off.

Functional Medicine has a Long History of Focusing on Gut Health

JB: Yes, fascinating. I'd like to take you back, say 25 years in our evolutionary history in the functional medicine milieu, and talk about two terms that I think were—at least to some extent—birthed out of those discussions that we were all having in the formative years of the Institute for Functional Medicine and the functional medicine model, and those two terms were "dysbiosis" and "leaky gut." Now, when those were first being used, as I recall, by those of us who were trying to put some legs under these concepts, we were pretty heavily criticized for these concepts. You know, what the heck is leaky gut? And, there is

no such thing as dysbiosis. Could you kind of give us some operational definitions of those terms and what they mean and how they have evolved?

RR: Well, certainly. I have to say that I really identify with that experience you're describing in the early days, and I think saying we were criticized is putting it lightly. I remember 20 some years ago getting a letter from an insurance company that had requested my records in my clinic and used both of those terms. They wrote me a letter that said basically that everything I was doing was fraudulent because I was using these terms that were developed by this Dr. Leo Galland and that everyone knew that these were made-up concepts, that they had no basis in science whatsoever. I remember feeling the sting of that years and years ago, and I also feel extremely gratified now to know that these terms are widespread in the medical literature, they are in mainstream articles that are appearing almost every day now. So it has totally become legitimate science; no one questions it whatsoever. Maybe some old-school gastroenterologists that haven't been to a library in a while might question this, but this is a very proven concept.

Dysbiosis, I learned about it from Leo—this whole notion that it's not just having a single pathogen that is causing an acute illness, but rather an imbalance of the microbes in the gut—so disordered life, really. I have found this to be such a tremendously useful concept over the years. Even though we didn't have very clear markers to show this was true—it was hard to prove it—but it was one of those things that you knew it when you saw it. I would say even all cases of irritable bowel syndrome are clearly a result of dysbiosis. Cause and effect we don't know, but dysbiosis clearly accompanies that. There is a problem with the microbiome in gut IBS, there's a problem with the gut microbiome in IBD, so it's this theme that carries through in a lot of intestinal disorders. And it has been expanded to include other areas of the body. In fact, I credit Alex Vasquez for using the term multi-focal dysbiosis to describe dysbiosis in, say, the sinuses or in the skin or in the mouth. We know that periodontal disease, for example, is not really an infection per se, as much as it is an imbalance of bacteria in the mouth that cause an inflammatory response.

Now the real question of where all of this stuff is going is now that we can identify a lot of the bacteria we're being asked the tough questions of what are the clear markers that indicate the dysbiosis. There is no doubt that the syndrome exists, but again, we're having to do the hard work of being able to come up with really clear consistent markers that will say, "Yes, this shows it." Is it low diversity? Is that an adequate marker for dysbiosis? Is it the appearance of certain bacteria or the lack of certain bacteria? If you have low levels of fecal bacteria, for example, or Akkermansia mucinaphila, is that an indicator? We went from the early days of thinking it was all about Lactobacilli and Bifidobacteria, and now we're realizing those are good players but they are relatively minor players when it comes to commensal bacteria. The bigger picture is going to be to ask: What is it that is missing or what is it that we have too much of that really defines the syndrome?

And then there's the whole notion of leaky gut, which again I think we have to thank Leo for promulgating this idea. It was never made up; there was always research showing that you could do a lactulose-mannitol test and demonstrate increased permeability, but that was a fairly obscure test at the time that people just simply didn't know about. It wasn't that the science was bad; it just wasn't widely recognized. But the clinical syndrome that was typical for that was the person that would say, "I eat a certain food and then two hours later my joints ache," or "two hours later I start getting this skin rash." So we knew that there was this relationship between food and systemic symptoms, even though we didn't

quite understand all the mechanisms. And then it was much later that Alessio Fasano came out and beautifully elucidated what all the mechanisms were, the whole idea of tight junctions opening up, translocation of all kinds of antigens from food and bacteria setting off an inflammatory response. So we've gone from this kind of crude notion that leaky gut is this observed clinical phenomenon, to now being able to quantify it, to determine what brings it on (things like gluten, or NSAIDs, or alcohol), and how to treat it.

Tests and Assays for Evaluating Gut Health

JB: So that leads to a question I'm sure is on a lot of people's minds if they are just getting into the field, and that is are there any tests or any assays or evaluative tools that you have found useful for understanding better dysbiosis and/or leaky gut? You mentioned the lactulose-mannitol test, but from a clinical perspective how do you feel about various types of tests that are available to define some of these parameters?

RR: Well, I do a fair amount of DNA analysis of stool. I will admit that we probably still have a ways to go before we completely know how to make sense out of that. People like Rob Knight have said, "Well, I don't think this testing is ready for prime time." But he's not a clinician. I'm a clinician; I need this information. I need to start somewhere, and I think we've really come a long way from doing these basic stool cultures where we're just looking for pathogens, we're looking for how much growth we get of Lactobacilli, Bifidobacteria, to being able to look at the overall spread. Now that we can look at the overall spread, then I think we can make certain assumptions about whether dysbiosis may be present or not. We need to come together as practitioners and researchers and have a consensus about exactly what constitutes dysbiosis. We're not quite there yet, but at the same time I think when you see it you know it. You know what I mean?

JB: Yes.

RR: It's a pattern, and the pattern doesn't always look exactly the same, but there is a recognizable pattern that I think can identify dysbiosis. As far as the leaky gut, I think lactulose-mannitol is still the gold standard. There are other groups that are using similar large molecules. There was a very interesting published study on Parkinson's disease that you might be aware of, where they gave sucralose and they used sucralose as an indicator. And the interesting thing about that study is that the researchers concluded that Parkinson's disease may actually start in the gut because they found leaky gut is one of the first signs that something was wrong and it correlated with alpha-synuclein build up in the gut neurons.[3]

JB: That is fascinating. So this whole gut-brain connection is just a remarkably evolving…I would call it tributary off this field that we've been working on for 25 to 30 years. It's really fascinating. Okay, given all of this, this sounds pretty darn important. Then how do you approach personalizing a therapeutic intervention to managing dysbiosis and leaky gut? Where do you even start?

Dietary Change is Still the Best Therapeutic Intervention for Gut Microbiome Imbalances

RR: I think the most compelling research has been on dietary change. I think we still don't have all the answers yet, but I think when you look at the data that is out there it's pretty clear that making shifts in the diet can have huge effects on the microbiome in just a couple of days. Rob Knight's lab did a very

interesting study where they had people do a Doctor Oz cleanse, where they made green smoothies and then I think they took high doses of a probiotic, and sure enough they were able to make some pretty profound changes in people's guts in just three days.[4] Very profound changes with a movement toward some very healthy bacteria. For example, they got big jumps in Akkermansia muciniphila, which is one of the healthier bacteria in the gut. Which is interesting because the probiotic they were taking—it was DSL #3; it's a very potent probiotic but it's mostly Lactobacilli and Bifidobacteria—but what they saw was not so much a big jump in those two bacteria, but instead things like the Akkermansia, so that's telling us that maybe probiotics don't do exactly what we thought they were doing. It's not so much that you have a deficiency of Lactobacillus acidophilus and then you take that bacteria and that makes the Lactobacilli grow. Instead it seems to improve the overall ecology of the health to take these beneficial bacteria. So there is probably a lot of interactions between all the different bacteria in the gut, and then what emerges is this healthier pattern.

You know, the confusing issue here is that we have this movement toward Paleo diets and telling people to eat fewer carbs and in many cases people are seeing a lot of benefits from Paleo diets, and yet some of the research that's been done, in particular a study that Peter Turnbaugh did, showed that when people went to these all-meat diets that were high Paleo diets they started growing some bacteria that weren't particularly healthy. I think one of them was called—I recall vaguely—maybe Bilophila wadsworthia or something like that?[5]

JB: Yes.

RR: That lives off bile? So that was a slightly foreboding finding, I thought. Whereas I think it is maybe going out on a limb to say this, but Michael Pollan basically has told us that eating plant-based diets is the healthiest thing, and the microbiome research tends to support that, tends to show that eating a wide range of fibers is really one of the best things for growing the healthy bacteria in your gut and preventing dysbiosis. So we're moving toward answering this question of what's the best diet for your microbiome? As opposed to what we've looked at in the past, which was what's the best diet for maintaining cardiovascular health? Or joint health, etc.? But now that we can test the microbiome, we can put people onto different diets and see. If I sound a little hesitant here, the reason that there is a bit of concern is that we also have people that don't digest carbohydrates very well and get a lot of gas and bloating and actually develop SIBO, and here we are telling people to go on a low FODMAPs diet, which would seem contradictory. Something that I see all the time in my practice, people that have low short chain fatty acids on a stool analysis, specifically low butyrate, and yet they get a lot of gas and bloating when they eat the very things that would be presumed to increase their butyrate. Cant's eat the FOS or the inulin or those other kinds of fibers, and so I think the challenge that is on us right now—the docs that do nutritional medicine and the nutritionists that work with us—is to be able to come up with some really creative ways to help develop healthier microbiomes in people without causing these problems.

Clinical Experience Using Prebiotics

JB: I think you've really done a superb job of defining the landscape in which we find ourselves clinically. That's really clear, excellent. A lot of what we're talking about just for the sake of terminology as it pertains to these nondigestible carbohydrates—these fibers—is often called prebiotics, and you've mentioned fructooligosaccharides and inulin, and larch arabinogalactans is another member of that family. Have you found, clinically, that you can vary the types of these prebiotics, these non-

digestible fiber materials and get different effects on your patients?

RR: I think for people that don't have trouble digesting prebiotics it is probably the single most effective intervention for producing the healthy microbiome. So, yes, there's no doubt that this is a great way to go for a lot of people. The question is what about that subset of people that don't tolerate them very well and so the search is on. I've learned a lot about dandelion greens, which are a pretty good digestible source of prebiotics, so I've been recommending those a lot more lately. It turns out that butter is a really good source of butyrate, especially ghee. I find that now that we've kind of moved away from the low fat diet craze and butter is okay again that putting people on ghee is the way to go. I think there is some evidence that resistant starches, like the resistant corn starch, may be useful. Frankly I'd like to see the dietary supplement companies move more in that direction—make more prebiotics that are easier to tolerate and easier to digest. I think there's a hole there that we need to move toward.

JB: Yes, thank you. What about phytochemicals/botanicals? Have you found that there are certain members of that family that have influence on modulating the gut microbiome?

Clinical Experience with Phytochemicals and Botanicals

RR: Yes, I think there's a pretty good body of research on all kinds of polyphenols. Even something as simple as grapeseed polyphenols added to the diet can be quite helpful. I use the whole range of those.

JB: We think of things like curcumin, or EGCG. Do these have any adverse effects on the microbiome or are they at least neutral if not positive?

RR: Well, it's kind of a million dollar question, isn't it? Some people have said, "Well, wait a minute. Curcumin does have antimicrobial effects." And another one that is in that same category is berberine. We've used berberine, this plant alkaloid that's found in goldenseal, and Oregon grape root, and Coptis chinensis—we've used that for a long time to treat dysbiosis, to treat overgrowth of Candida albicans and other yeast, to treat parasites, and yet now there is this emerging interest in using it for metabolic syndrome, and one of the theories about why berberine is so effective for metabolic syndrome is that it actually regulates the microbiome. It may help to suppress unhealthy bacteria and allow the growth of healthy bacteria. But that's created a bit of an argument because some people say, well, an antimicrobial is an antimicrobial; it doesn't matter if it is berberine, or garlic, or green tea, or curcumin, or oregano oil. It's still an antimicrobial and that could potentially create a problem in the long run. Well, I've had people on berberine for years. I've taken it myself for years. And I haven't had any negative feedback from people. There are always going to be people that have initial reactions to just about anything you put them on, but I haven't really seen it to be problematic. That being said, I still think it's a good idea to use probiotics whenever you're using these compounds because I just think they work well together.

Endotoxemia and Inflammation

JB: Yes, that's really a good clinical pearl. So let me shift slightly to another term that has become much more prevalent in the literature and I think it explains a lot, this term, once we understand it, and that's the term "postprandial endotoxemia." Could you give some definition of that and what it means and what we do about it?

RR: Well, endotoxins are another word for lipopolysaccharides. They bind to the toll-like receptor-4. I think that's a big part of the mechanism, and toll-like receptor-4 is one of the most inflammatory transmembrane receptors in innate immune cells and other cells. So if you really want to upregulate the immune system, do it with endotoxins, you know? You want to boost the immune system? Endotoxins are the way to do it except that they may boost your immune system so much you go into endotoxic shock. Now, in the early years we only thought of endotoxic shock as being an all or none phenomenon—a very severe situation that would be life threatening. What we've realized over the last decade or so, I guess, is that every time we eat there is translocation of endotoxins, and that there are certain foods that seem to be particularly conducive to creating this scenario. The famous example of that was the McDonald's Happy Meal. You know? Where it was shown that if you gave people a McDonald's Happy Meal that has that mixture of a lot of saturated fat, and French fries or hash browns, that that clearly increases circulating endotoxins. And the whole problem with that is that those endotoxins are then binding to toll-like receptor-4 and other inflammatory receptors all over the body so you get this low grade systemic inflammation. Of course that can go down in many different directions depending on the susceptibility of the individual. In one person it might lead to polyarthropathy (inflammatory joint disease). In another person it may lead to atherosclerosis. And in yet another, metabolic syndrome and obesity. This appears to be a core phenomenon that's really of great concern. The question is what can you do about it? The obvious thing is to cut back on the Happy Meals, if that's the inciting meal, and we know that this mixture of fried carbohydrates and saturated fats seems to be particularly bad for doing it. It would be nice to have good clinical tools that we could use to find out whether other meals are doing that. If you eat a baked hamburger that's not cooked at too hot a temperature, is that also doing it? In order to be able to do that we've either got to be able to measure circulating lipopolysaccharides or get a quick LPS antibody test, and those tests are on the way, but I think ideally we would have something like that available in a clinician's office to do a quick test so we could say, "Yes, this intervention is going to make a difference." And that gets us back to, well, can we use L-glutamine, for example? If we make the enterocyte healthier by giving them their primary fuel will that decrease the amount of translocation? So there are questions that are arising as a result of these observations.

JB: Bob, you just defined a really, really wonderful little teaching metaphor that I know all of us have used. I really give attribution to Dr. Sidney Baker who is another one of the master teachers in our functional medicine core group, and he talked about that the principal concept in medical therapeutics is to remove things that are doing harm and to replace things that are necessary (replace the things that are missing).

RR: Yes.

JB: And so you've really talked about that. You're talking about let's remove the stuff that's not so good, and then on the other side if you've got these endotoxins like LPS that get in the blood and other maybe debris—other small molecules that would be considered metabolic toxins—then it begs, on the other side, what goes on in the hepatobiliary system that's going to block those from getting access to the rest of the body. So then we get into the detoxification system, which you have been a leader in for many years—this whole cytochrome P450 mixed oxidation Phase 2 conjugation systems, and also the interrelationship with gallbladder bile acid secretion, which is important. Tell us a little bit about how that fits into the schema as you manage patients?

RR: Well, I tell you, the numbers that I'm seeing out there for fatty liver—the estimate—is maybe 20

percent of the population? Is that what you're seeing as well?

JB: Yes, yes.

The Gut-Liver Connection

RR: Where is that fatty liver coming from? A lot of people think it is a direct result of this endotoxemia; that the liver is getting the brunt of all of these endotoxins, it's creating an inflammatory problem, and that's causing lipotoxicity (an accumulation of all kinds of fats) in the liver, which then leads to a wide range of problems. Certainly putting the attention on making the liver more effective, keeping the glutathione levels up in the liver, I think is a really good way to do that. And we know how to do that. We've gotten a lot of data over the years of how effective things like n-acetylcysteine, alpha-lipoic acid, curcumin, sulforaphane—we've got a pretty good sized toolkit for raising glutathione in the liver, so I think that's one way to improve overall liver function, and you mentioned bile acid secretion. Curcumin both raises glutathione level and increases bile flow, so it's going to address this problem on two different levels and that makes it one of my all-time favorite nutrients to use for supporting the liver, helping prevent fatty liver, and the consequences of endotoxemia. And then there is the whole NRF2 pathway—the antioxidant response element on DNA that upregulates phase 2 enzymes. I think that's a really effective strategy, and now we know that there's this long list of things you mentioned. Green tea is great for upregulating NRF2; so is sulforaphane from broccoli sprouts, so is resveratrol, so is curcumin. So we have a pretty good toolbox for dealing with this once we recognize the problem. Our challenge is to get out there to clinicians and say, "Hey, this is not speculation. We've got really good data to support this gut-liver connection."

JB: So that then leads to a really interesting new branch of this theme which I find quite fascinating because it has many subtle implications about the whole nature of how we interrelate with the outside world, and that is the recognition that chenodeoxycholic acid and cholic acid (bile acids) are not just solely emulsifiers for fat, but they also have receptors, like the EGR-5 receptor that really activates signaling of the inflammatory and insulin sensitization pathways throughout the body, so it's raising this concept that digestion, as it pertains to fat digestion and gallbladder secretion of bile, is much more than just emulsification and absorption. There is something going on here that really triggers and signals to the whole body how genes are going to be expressed in various tissues that relate to inflammation and insulin signaling. Tell us a little bit about your thoughts on that emerging field.

RR: Well I don't know much about the specific receptor pathways that you're talking about. I do know that bile acids are appreciated as a two-edged sword. Certainly if you have excessive amounts of them then that causes an inflammatory scenario, but then you have to have them. I'm often asked, "What do you do for somebody who has had their gallbladder out? Is that a problem?" Well, we don't know. Nobody has done the studies to show that that can have long-term implications, but it raises the whole issue of whether the gallbladder is just a vestigial organ or not. Do you think it's a vestigial organ or do you think it's still serving a useful function? From what you're talking about, the implication is that we need it. Maybe we shouldn't so blithely take it out. Obviously if somebody's got cholecystitis or gallstones and they have to get it out then that's one thing, but maybe we need to consider the possibility. I've certainly used bile salts in people with liver disease and it's a very interesting way to go. I know there is some research at the University of Colorado using…I think it's lithocholic acid?

JB: Yes, that's right.

RR: This raises a lot of really interesting questions. There's really nothing that the body does that isn't useful. Something I often talk about at IFM is the body is a really elegant machine that has been evolving over a couple of billion years ever since the first microbes started fusing and forming multicellular organisms, so there's not a lot that the body does that doesn't have some rationale or some reason behind it.

JB: Yes, going back quickly to this bile story, there is a company called Intercept Pharmaceuticals that is now developing a drug, which is in phase 3, for the treatment of NASH (nonalcoholic steatohepatitis)—the fatty liver condition you were talking about—which is basically a modified bile acid that activates these receptors that I was alluding to that then control aspects of metabolism, both from an inflammatory perspective and from an insulin sensitization perspective. And Intercept is suggesting that this is a platform technology—that basically these drugs (these modified bile acids) will, in fact, be demonstrated to be effective in treatment of type 2 diabetes and a variety of inflammatory conditions beyond that of NASH. So I think your point that you're making about the magic of how things in the body have pleiotropic effects—that have not just one role, they have multiple roles, multiple personalities, and often we tag a substance in the body with a simple definition thinking we understand it, when we really don't yet understand all the multiple ways that it is influencing function across a broad range of different organ systems. And I think of bile itself as composed of cholesterol, bile salts, and lecithin, and that you can modulate the composition of bile, making it more or less soluble based upon how you eat, and certain dietary factors and certain nutrients. So the composition of bile itself can have very dramatic dietary implications, and that can then secondarily have huge effects on all sorts of systems, including insulin and inflammation. So I think that this web that we have been exploring and interrogating in the functional medicine model is where the mystery is, but is also where the answers, reside for many of these chronic problems.

RR: You know it makes me wonder about the old-time naturopathic remedy of using lipotropic agents (betaine, trimethylglycine, dandelion root, celandine), which are basically agents that help improve bile flow. It's fascinating that they're coming up with drug solutions for this and I'm just wondering if there are things we can do to induce the body to accomplish the same thing without necessarily having to go to a prescription bile salt analog.

JB: I absolutely agree. I think what we learn from pharmaceutical research is how the rationale of what we observed clinically from observational work with diet and lifestyle may work at the cellular level, and then from that we can tune those programs up using the natural balance points in physiology rather than overriding the system with one too strong a signal that we often get from a pharmaceutical. There is a symbiosis, I think, between understanding what's going on in the pharmaceutical world and then finding how that really gets applied properly in the body's rhythm—it's orchestration of function—with natural remedies.

RR: I couldn't agree more. I've learned so much from the drug companies. I mean really, they are great at elucidating mechanisms.

Increasing Awareness about Gastrointestinal Health

JB: Yes, exactly. Let me thank you. This has been an extraordinarily kaleidoscopic and interesting journey that we've been on, but let me give you a chance to be a little of a soapbox philosopher, which I know you are. So you're the 2015 Linus Pauling IFM Award winner. That comes with a certain pedigree of perspective. So what changes would you make in medicine if you were a Surgeon General, that would bring the functional medicine concept of gastrointestinal function and its relationship to health and disease into greater understanding and clinical application?

RR: So specifically how would I bring awareness of GI health?

JB: Yes, what would you do if the president said to you, "Dr. Rountree, I want you to find a way to incorporate these concepts into healthcare paradigm and practice." Would there be something you think is most important that we do to get that to happen?

RR: You know I would have to say I would probably start with birth practices, because that's where I think we are really going awry and I have to attribute some of this thinking to what Martin Blaser has told us about the more C-sections we have the more we lose generations of microbes that have taken billions of years to evolve. And so I think the first thing I would say to the Surgeon General is let's do some pretty extensive research about what's happening around birth with the microbiome so that we can start kids off with healthier guts that then can presumably have healthier lives and fewer inflammatory diseases, allergies, etc., because we have this huge epidemic of kids getting allergies and inflammatory bowel diseases are on the upswing. That's an area where if we can address the root cause of it by how the genesis of the microbiome is being impacted with birth practices that can make a huge difference for people. I think the other thing is that we need to get this concept out to the public about the importance of gut diversity—of biodiversity and intestinal microbes. And it's going to be a challenge to get that science across to people, but I think it's a message that once it's well-crafted and once we can translate it into some simple dietary things like eating less refined food, which Michael Pollan has been telling us—a lot of people have been telling us this—for a long time, but this is from the perspective of making your microbiome healthier, getting good fibers in your diet, getting a lot of greens in your diet. All these things are going to be good for your microbiome. I think those are two messages that I really want to get out there.

JB: Well, once again, for all of our listeners we want to thank you. There was a lot of wisdom in the last hour of discussion with you (a lot of experience and wisdom). And on a personal level I just want to thank you for 30-plus years of great friendship and collegial relationship. You've contributed a lot to me and it's been really a great pleasure to have the chance to be on this journey and watching this model evolve over the last three-plus decades.

RR: Thanks, Jeff. It's been great sharing this journey with you.

JB: Best to you, Bob, and keep spreading the news. I think the change is right in front of us.

RR: Yes, it's happening

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