

## May 2012 Issue | Frederick Timothy (Tim) Guilford, MD ReadiSorb Liposomal Glutathione

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Welcome to *Functional Medicine Update*, May 2012. Glutathione. Long word. A lot of implications. The most important intracellular antioxidant known in human physiology. An enigma in some respects, because we recognize that glutathione has multiple functions within physiology and therefore, as such, might be considered a pleiotropic molecule, meaning that it participates in multiple functions. We know it as a principal antioxidant, but we also recognize that it is involved in detoxification, to form mercapturic acids that detoxify biotransformed set intermediates that can be excreted in the bile or urine. We also recognize that it can conjugate itself with various substances like arachidonic acid metabolites to form lipoxins and other types of interesting compounds that come as a consequence of the enzyme lipoxygenase.

When we start looking at the multiple roles of glutathione in modulating leukotrienes, or modulating the oxidative stress and the redox potential of cells, or participating in detoxification, we recognize that it has a central important role as a cellular agent of cellular direction. It's a director of function. We also recognize that glutathione is biosynthesized as a consequence of functions within certain cell types where it is needed in high levels, like hepatic cells, by the construction of three amino acids: glutamic acid, and cysteine (itself or containing an amino acid), and the simplest amino acid of all, glycine. This gamma glutamyl cysteinyl glycine becomes a tripeptide that we know as glutathione. We recognize that gamma glutamic acid is not the normal way that the amino acid glutamic acid that is stuck together with other amino acids to make proteins. Normally they are acid amino acid linked, but in this case it is a gamma linkage, which is unique to the glutathione use of glutamic acid in the construction of glutathione as gamma glutamyl cysteinyl glycine.

We recognize that oxidative stress is a fundamental property of aerobic metabolism. All oxygen-breathing organisms, by the nature of their function, oxidize substrates with oxygen into secondary metabolites, ultimately going to carbon dioxide and water in humans. But along the road they may produce free radicals that are oxygen- or nitrogen- or sulfur-containing that could have damaging effects on cellular function. It's the regulation—it's keeping what I call the electrons on the wire and preventing them from jumping off the wire and burning the curtains, which we call the cellular membranes and the various materials that make up cells. This burning, or this singeing, or this combustion is known as oxidative stress and is credited with producing free radical pathology. And glutathione, in the centers of oxidative chemistry within cells like the mitochondria, is very, very important for maintaining proper control of these electrons that flow down the wire and don't jump off onto the curtains and create combustion in the house.

Glutathione is oxidized to its byproduct, glutathione disulfide, and glutathione disulfide is subsequently regenerated into glutathione with the enzyme glutathione reductase, which requires a reduced form of riboflavin, adenine dinucleotide. We recognize that the oxidation of glutathione to its disulfide doesn't occur just at random but occurs in the presence of a facilitator called glutathione peroxidase, and that is a selenium-containing enzyme. So this shuttle of glutathione's regulation back and forth between glutathione and its disulfide is a tightly controlled, energy dependent function that keeps the electrons on the wire. It's a very, very important switching point for the maintenance of what I call the voltage in the battery of our cells, our so-called redox potential. Where our car batteries need to be about twelve volts in order to start our motor more efficiently in the car, so does our electromotive force, or our voltage in cells, have to be maintained properly by the regulation of the redox potential that's generated out of the mitochondrial oxidative phosphorylation, and that is in part regulated through the personality and the function of glutathione in conjunction with many other cellular components of this redox engine. With that in mind, we start saying: What have we learned about glutathione? It's to that that we're going to have this extraordinary discussion with our clinician/researcher of the month this month, who I think has done a fantastic job, Dr. Tim Guilford. He has really been at the cornerstone of really starting to understand the glutathione story in clinical medicine. So with that in mind, let's move over to our clinician of the month.

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### INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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I had the good fortune, at the recent College for the Advancement of Medicine meeting, to have a personal discussion with a physician/researcher in our field that I think is really doing something very, very interesting that I believe all of you will be interested to find out about, and that's the work of Dr. Frederick Timothy Guilford. I'm going to say "Tim"; that's the name that he goes by. Tim did his undergraduate work at Johns Hopkins and then his medical doctor work at the University of Texas Medical Branch at Galveston, a very good institution. One of our previous FMU interviews, Dr. Victor Sierpina, is on the faculty at the University of Texas Galveston and is in charge of the family practice residency program there, so we have a good kinship with that institution. Tim presently is in practice in Los Altos, California and I also have a kinship to Los Altos, having spent a couple of years at the Pauling Institute. I moved down with my family to Los Altos Hills, a beautiful part of the world there

in northern California. Tim has been engaged in a variety of different clinical intervention-type programs, particularly focused on things like heavy metal detoxification related to mercury and other heavy metals. But through that work he has also become very, very much the expert in a nutrient, or a conditionally essential nutrient, that we are all very familiar with and one that we can never learn enough about because of its central importance in human physiology, and that is glutathione. Certainly if we were to do a search of the times that I've mentioned glutathione over the 30 years of doing Functional Medicine Update the result would be a laundry list of discussions about this very important substance that is, as you know, a shuttle in the electron transport chain in mitochondria. It plays a very important role in a whole series of functions related to redox potential of cells. And it is also a very strong chelator as a consequence of its sulfhydryl moiety that is one of the three amino acids that makes up glutathione, the cysteine residue. With that as an introduction, Tim, welcome to Functional Medicine Update and thanks so much for being with us at a time where the discussion of glutathione couldn't be, I think, more important. Welcome.

FTG: Thank you very much, Jeff. It's really a pleasure to be here.

JB: Tell us a little bit, if you could, about your practice and what led you into this whole area of heavy metal concern, detoxification, and ultimately into this focus on glutathione?

Glutathione and Heavy Metals

FTG: I've had a lot of fun in my clinical practice. I started in practice around 30 years ago, and had the experience of not only practicing as an ear, nose, and throat surgeon, but became the director of an allergy and immunology lab. That introduced me to a wide variety of individuals and medical approaches, and one of them was dealing with chelation, or heavy metal detoxification, and in the mid-90s some of the lab testing came out with improved mercury testing. So I went to the library to find out what made mercury toxic, and the first article that I ran across was an article by a fellow named Stohs, who had written about heavy metals depleting glutathione.[1] This was about 1996. At that time I had only a superficial knowledge about glutathione, and as I started reading about it I realized that it played a critical role in both immune function and also in detoxification, and that led me into glutathione research. I became addicted to reading about glutathione, if you will. There are almost one hundred thousand articles out there with the key word "glutathione" now, so that's what started me on the path of research in glutathione.

JB: I find it really interesting when I look at your resume and talk to your colleagues about what separates certain people that have an intellectual curiosity that move on to where it becomes just a burning part of their pursuit of understanding and other people who may just kind of move on and say, "Well that was an interesting thing for the day but it's not worthy of my attention at the deep level of pursuit." In your case, obviously, this has become a very, very important part of your continued pursuit and understanding, and really becoming, I think, arguably one of the most significant experts in this area. In fact, as I recall, you won the Norman Clark award for your work in this mercury detoxification area, and I share that years ago I was a recipient of the Norman Clark Award as well, which I take with great pride. So that illustrates, I think, a very strong leadership. Tell me how, since that 1996-97 period, you've kind of pursued this to the level that most people don't. Because you've ended with a technology, with an understanding of some of the difficulties of glutathione as a therapeutic, and maybe how to overcome some of those therapeutic difficulties with different technologies.

A Liposomal Delivery System Allows for Oral Ingestion of Glutathione

FTG: Early in the days of my research into glutathione we were using, basically, the building blocks of glutathione. You mentioned earlier the three amino acids that form the tripeptide—glutamine, glycine, and cysteine—and at the same time as using the building blocks, especially materials like n-acetyl-l-cysteine,

we were also able to give glutathione intravenously for a number of conditions that are associated with low glutathione, and occasionally we'd see very dramatic improvements, especially in older people with Parkinson's disease and occasionally in children with autism, and it became clear to me that we needed to have some way to get the reduced form of glutathione into the body on a regular basis. About seven—almost eight—years ago now, I was very fortunate to find a manufacturer who understood the delicacy of putting glutathione into a liposome. A liposome both keeps the glutathione stable in the reduced (that is, the active) state, and also allows some improved absorption so that we're able to get glutathione into the system, for the first time, orally. Having the opportunity to get glutathione into the system clinically began to show some real value, so I started on a path where I was fortunate to be able to develop the product first and then I have been pursuing research to demonstrate its various properties since that time.

JB: I think that's a great segue. Let's back up and make sure everyone is coming down this road with us together. So you talked about reduced versus oxidized glutathione. Let's start there. What's the chemical difference between those two and are they both bioactive, and how do you know what form of glutathione you have, reduced or oxidized?

#### Difference Between Reduced and Oxidized Glutathione

FTG: Basically, the difference between reduced and oxidized is the availability of that hydrogen atom on the sulfur (prominent sulfur) that makes up glutathione. The molecule glutathione creates a platform with the cysteine portion containing sulfur sticking up out of it. In its active state it is able to donate the electron and the proton, the sulfur, to various chemical reactions and that's what allows it to have what's called a very strong reducing action, meaning it can donate this electron. The platform of glutathione is what makes it unique. It's very stable inside the cell, where other peptides are degenerated, and it allows it to interact with enzymes such as glutathione peroxidase, and another one called transferase. These are the key components of its antioxidant and detoxifying function. When it is oxidized (that is, it gives off the proton hydrogen and the electron), it has a preference to bind with another glutathione, so the molecules are still available, they're just not as biologically or biochemically active, and they can be returned to this active state by interaction with other antioxidants like vitamin C, or through an enzyme mechanism through glutathione reductase, which will separate the two oxidized molecules and create the two molecules of reduced glutathione.

As far as telling which ones you have, it would require some biochemical testing, for example with our Readisorb™ Glutathione we test each batch and we have followed it along chronologically to be sure it is indeed staying in the reduced state. We've been very pleased to find that it is very stable.

#### The Two Primary Roles of Glutathione

JB: I think, again, you are doing a marvelous job of helping fill in some of the gaps for us. Let's talk about these two kind of schizophrenic or pleomorphic roles that glutathione has that you mentioned. One is, in its redox capabilities, maintaining redox potential in the cell, which sometimes we call its antioxidant properties, and the other is its detoxifying properties. So the enzyme that you mentioned relative to its detoxifying capability, glutathione s-transferase, that enzyme as I recall is highly polymorphic, meaning it has a lot of genetic variability, and I think there are certain states of that, certain single-nucleotide polymorphisms (SNPs), that make it what's called the null mutant, that it doesn't work very well, and therefore those people may be slow detoxifiers relative to the ability to conjugate glutathione with biotransformed intermediates to form these mercapturate byproducts. Is there any way, by increasing the cellular concentration of glutathione, that you can kind of force that sluggish reaction in

a person who has a slow glutathione s-transferase activity?

FTG: I think you can. I like to refer to glutathione s-transferase as the matchmaker. This means that the matchmaker is introducing glutathione to a toxin. That way it facilitates glutathione sticking to that toxin, which allows it to be excreted out of the cell, through the blood, to the liver, and out through the gastrointestinal tract. That's the mechanism for removal for a lot of toxins and mercury a prototype of that, for example. As you mentioned, there are several different forms of glutathione s-transferase, and we can refer to this as GST (that's the usual abbreviation that you'll see in print). There are several forms of the GSTs, and up to 40 percent of the population can be deficient in the ability to make some of these different forms (scientists call them isoforms). When this happens, glutathione is still able to interact with a large number of the majority of the toxins that it needs to work with, but in my opinion you need an increased number of molecules of glutathione to allow this interaction to occur. Again, back to the matchmaker: you need more encounters to find the right match (to continue that analogy). We have seen individuals with documented GST SNPs in which they don't make the isoforms as efficiently. Many of them feel better by having an increased number of glutathione molecules available using the oral liposomal glutathione. But those are anecdotal observations at this point, but it has been very gratifying to be able to help many of these people.

JB: So let's now look at the other side of the equation, which is the antioxidant or redox capability of glutathione. So you talked about glutathione reductase and glutathione peroxidase being enzymes involved with that shuttle. Are there situations where there has been a compromise in glutathione status, knowing that it is the principally most important intercellular antioxidant, and I think, as I recall, the ratio of the reduced-to-the-oxidized glutathione in healthy cells is something like 100-to-1 (100 of the reduced to one of the oxidized), so if you start getting a shift in redox and you get less of the reduced and more of the oxidized that means the kind of voltage of the battery of your cell is running down. Can you improve that, then? Just as we talked about detoxification improvement with glutathione addition can you improve the redox potential of a cell with glutathione addition or support?

FTG: I think you can. It's a little more difficult to demonstrate the electrical side of that, but we have a published study showing that cells exposed to materials like maneb and paraquat, which cause oxidation stress inside cells—these are materials that have been used as pesticides in the past; happily they're not being used as much now, but there is still some usage. Neuro-researchers, for example, use this to cause oxidation stress inside of cells. We have an article showing that the oxidation stress can be limited and diminished significantly by adding the liposomal glutathione.[2] And I should also point out that the use of any antioxidants in general, ranging from vitamin C and vitamin E, and including N-acetylcysteine, which help build the tripeptide glutathione and these other materials, the antioxidants help maintain the reduced state, these are all critical components of maintaining reduced glutathione in the cell. We have some information coming out from our research that shows that there are certain situations where it is difficult for cells to make the tripeptide glutathione, and in these cases there is some advantage to adding the intact molecule of reduced glutathione to the cell in the liposomal glutathione.

JB: So let me, if I can, now ask the question which is probably on the minds of many of our listeners, and that is: "Okay, well you've certainly done a good job with your explanation in demonstrating why conditionally essential glutathione might be beneficial to supplement. Why can't we just give glutathione itself? What's the problem with just administering high doses, orally, of glutathione?"

FTG: It turns out that most of our cells have an enzyme on the outside of the cell called gamma glutamyl transferase. You have to remember that most of these enzymes and biochemical molecules were named when they were found and their full usage became apparent later. The glutamyl transferase, often abbreviated GGT, and incidentally is available on your routine chemistry panel now, plays a role in breaking down glutathione. It sits on the outside of every cell, and particularly in the gastrointestinal tract

of humans, and it breaks down glutathione into these three amino acid component parts. Then the cell can take up the materials and reassemble them inside the cell, which sounds useful, but it turns out to be not very practical, and doesn't really replenish the levels of glutathione as efficiently as we would like. You have to remember that reassembling these molecules, especially in a stressed cell, requires energy and various interactions like that can become compromised in a very stressed cell. The enzymes need to work very efficiently. There are two enzymes that piece these three amino acids together, and if you don't have the right amount of energy, and the right amount of the enzymes, you don't get the glutathione reduced as efficiently. So, that's the major problem with taking plain, non-formulated (as we sometimes refer to it) glutathione orally.

JB: So let's, Tim, go from there, then, to talk about what I consider a very remarkable and laudatory step that you've taken. You know, most clinicians who have the level of inquiry that you have, which is, in itself, quite remarkable, get to this point of understanding and then might put up their hands and say, "Well, I just don't know how to solve the problem. There's a block here, but I'm not sure what the solution is." But somehow you took it to the next level. You worked on this formulation, and you've actually been involved now, as you mentioned, in work that has ultimately led to publication. This recent paper in *Neurochemical Research* that has your name and your co-colleagues on it from the department of neurology at the Robert Johnson Medical School in New Jersey is an illustration of going to the next level. Tell me how you did that, why you did it, and what the outcome was, because I think this paper titled "Liposomal Glutathione Provides Maintenance of Intracellular Glutathione and Neuroprotection in Mesencephalic Neuronal Cells" is a very interesting advance from hypothesis to proof.

FTG: Well, thank you very much. I appreciate it. At first I was just slow in terms of understanding biochemistry, meaning I had to read it a lot to hold the information. As an aside, I went through various detoxification procedures myself to lessen the mercury load in my brain, and I think it allowed me to understand this a little better, perhaps from the practical side. I became really interested in the mechanism, and there were so many interactions it became fun for me. It was a bit like relearning medicine, being able to follow the roles that glutathione plays. I spent six months in a lab over at Stanford that's known for its work in glutathione, the Herzenberg Lab, and then I began pursuing some more research, and the paper you mentioned by Gail Zeevalk in regard to the intercellular glutathione and neuroprotection was started by a chance interaction after I read Dr. Zeevalk's 2008 paper, in which she was writing about Parkinson's disease. The title of her paper was "In the Discussion of Parkinson's Disease, Is Glutathione the Elephant in the Room?"[3] Meaning, it is really difficult to talk about Parkinson's without talking about the fact that glutathione is depleted in the specific brain cells, the substantia nigra cells, which are responsible for the production of a continuous supply of dopamine to maintain movement.

Dr. Zeevalk had set up a cell culture model in which she was able to demonstrate that cells depleted of glutathione, using a binder material that would remove glutathione, could be repleted with plain glutathione at a about a concentration of 500 micromolar (if you put 500 micromoles in the cell culture you could replete these cells efficiently). They call that "to the effective concentration." I sent her emails and eventually we had a phone conversation and she said, "If you think your product works send it out and we'll test it in the cell culture model." It turns out that where plain glutathione took 500 micromolar, it took only 5 micromolar of the liposomal glutathione to replenish these cells. Dr. Zeevalk went on to do a series of studies demonstrating that the glutathione is contained in the liposomes, doesn't leak in the cell culture, and the whole liposome molecule is absorbed right into these brain cells. Incidentally, the mesencephalic cells are made up of astrocytes and neurons, and it is primarily the astrocytes that are engulfing the liposomal glutathione. That also points out the roles of neurons, as Jeff knows, are very specialized in their function and they actually are fed glutathione from the astrocytes in the anatomic

situation, so being able to get glutathione into the astrocytes in an efficient fashion using the liposomal glutathione may have some real advantages.

JB: Tim, you've really opened up a very interesting journey with us that I'd like to follow up on, so let me go back, if I can, to pick up your first discussion about paraquat as a chemical that can stress cells and deplete glutathione. I'm reminded of my own experience in 1982 when I was at the Pauling Institute. That was a time when there had been reports that individuals in the San Francisco bay area who had been using a certain form of marijuana were coming down with a high frequency of Parkinson's symptoms, and then they ultimately traced this back, as I recall, to the fact that the source of the botanic marijuana were fields that had been sprayed with paraquat and that they were actually being exposed to this substance that was inducing in them, through the administration of marijuana, this Parkinsonian syndrome, and they ultimately used that actually as a way of assessing this oxidative stress component of the disease. It is interesting how things run kind of full circle, because then we segue fast-forward to Dr. David Perlmutter, who we both know as a colleague in our field and who has been a Functional Medicine Update interviewee a couple of times over the last 30 years, and his observations in clinical practice as a neurologist by intravenous administration of glutathione, the remarkable improvement in symptoms he's had in patients. Unfortunately it doesn't seem to last; it has a short-term duration. But it certainly does open up, as you said, the question as to what role does glutathione play at a supraphysiological level in individuals that have undergone maybe significant oxidative injury at the nigra striatum and who have high oxidative stress and depleted redox. Then you come back to this wonderful work you've done in culture with Dr. Zeevalk and demonstrate actually in a cell model that you can, by increasing in the medium the appropriate absorbable form of glutathione, that you can actually produce outcome in the cells that are reflective of what we see physiologically in the whole animal and maybe even coupling it back to the 1980s observation of the use of this paraquat-tainted marijuana and Parkinson's. It sounds to me like there is a very fascinating clinical story here that probably moves on, then, into your interest in other neurodegenerative conditions like, say, autism, and probably a variety of other toxic situations that lead to the depletion of glutathione. Am I making sense here at all with the way I'm describing the story?

FTG: It does to me. What has been most interesting to me is how exciting it is to explore these various pathways and various applications. A friend of mine, Professor Ben Lucchesi at the University of Michigan, has mentioned the fact that when you are exploring these pharmacologic and biochemical interactions it's a lot like puzzle solving and being able to see the solutions for some of these problems has been the real motivator for me. One other note on the paraquat plus maneb, it turns out that these SNPs that you were mentioning earlier in regard to the GSTs can also be at play in regard to some of these pesticide problems because maneb, for example, is broken down by certain hydrolases, which there can be varying levels of their representation in people, and if you don't have as much of these enzymes available you may be at greater risk, but then you need that heavy environmental exposure to increase the chance of problems like Parkinson's developing. It points out the interaction between environmental exposures and the individual's ability to detoxify that may play a role in a number of conditions, and you mentioned autism. The exploration of that problem was a real stimulator for me. A researcher named Jill James published a paper in 2004 which described for the first time the fact that children with autism are poor methylators, meaning they don't methylate or stick a carbon onto the important biochemical involved in a cycle called the methionine cycle.[4] That's the one that takes methionine around in a circle, creating homocysteine, and returns the homocysteine back to methionine. That cycle is important for glutathione research as that cycle will produce the cysteine that's the rate-limiting factor in the production of glutathione. I should mention that those two enzymes that are involved in the production of glutathione. When you have cysteine, there is one called glutamyl cysteine ligase, which will combine cysteine and glutamine, so you have two portions. And then the next one, glutathione synthase, will stick

the third amino acid on there to create the tripeptide. It turns out there are certain conditions and situations, especially heavy oxidation stress, which can compromise these enzymes as well as the transcription factors controlling these enzymes. So all of a sudden this world of information is kind of blooming up on the horizon that is going to help better explain why certain children with autism and certain individuals who develop Parkinson's are more at risk than others.

JB: I think that was brilliantly summarized. That's a very complicated area, but you've done a marvelous job of summarizing it. In fact, we did interview, for Functional Medicine Update, Dr. Jill James in the wake of her publication. Her continued work in this area is, I think, really kind of pioneering. It seems to me, once again, as I introduce the topic of glutathione that there is a thousand points of contact of this very important intermediary, and the concept that it could be a conditionally essential substance or nutrient in some cases is a very, I think, powerful concept.

What is a Liposome?

Let's now go to the story of the liposomal delivery system. The term "liposome" for some may be not such a familiar term, so I would like you to describe what a liposome is. And secondly, there might be a variety of different kinds of liposomes that have different characteristics and so why is the liposome that you have pioneered the superior delivery form? Why this specific one? Those are my two questions.

FTG: As I said earlier, I was fortunate to find a manufacturer that has experience in encapsulating materials in a liposome. You can think of a liposome as a small fatty bubble. The ones we use are, on average, around half the size of a human hair (500 nanometers). The process that is used actually in this case uses a very unique liposome and process that allows it to encapsulate the water soluble glutathione inside, usually in a single layer, but sometimes multiple layers of these very thin layers of liposome, and it creates this little fatty bubble. The big advantage was the fact that you could take these liposomes orally. We've known for a long time that the glutathione itself was not utilized if taken orally as efficiently as we'd like. There was an assumption—and I think a correct assumption—that most of the liposomes you take orally are not well absorbed. It is clear from our research we've documented in other studies absorption and tissue function in animal studies, and incidentally we have some ongoing research in that area that demonstrates increases in both heart and brain tissue, for example, but being able to take orally the liposome and demonstrate an action in distant tissue has been the real advantage with this material. And it begins to open up investigation into a range of conditions that are associated with low glutathione.

JB: When I look at this really interesting paper that was recently published in 2012 (January) it talks about the difference between a liposomal (your ReadiSorb Glutathione delivery) and a kind of normal glutathione preparation, and shows, using a cobalt isotope assay in the rodent, superior intracellular incorporation.[5] Is this the kind of assay system that can be useful, from your experience, in actually evaluating how these comparative delivery systems might work in humans?

FTG: I think it would be very useful. I guess the disadvantage of doing it in humans would be getting them to take the radioactive material. In the rats, they were given an intravenous infusion with radioactive cobalt. Cobalt is known to be bound by glutathione. In this particular study that was done by Dr. Levitskaia at the Pacific Northwest National Lab, where they specialize in radiation and radiation remediation techniques, they showed that the oral ReadiSorb liposomal glutathione has about 75 percent of the function of the intravenous-administered glutathione, while the plain glutathione which we were discussing earlier (the difficulties in getting plain glutathione to be absorbed), the plain glutathione in the rat had minimal function in terms of removing the radiotag cobalt from the liver of these animals. So we were very gratified to see that the orally administered liposomal glutathione can be absorbed and have a similar function to IV glutathione. Of course the advantage in that situation is that you can take the

glutathione daily or several times a day depending on the situation that you're dealing with. That, again, is both illustrating the utility of the material, and then as you have pointed out, opening up a variety of lines of research that are really quite exciting in terms of solving these different puzzles.

JB: Let's close with probably what a lot of people at this point are asking and that is: "Okay, we've talked through the importance of glutathione, we've talked about comparative delivery systems, we've talked about the advantage of this particular liposomal delivery system that seems to promote cellular uptake, so now what is your experience, or anecdote, or experimental experience with the human administration with this liposomal system? What doses are effective and what kind of things have you seen as it relates to its application?"

#### Anecdotal Results of Clinical Use of Liposomal Glutathione

FTG: Well, I'd like to remind everybody that we don't make any claims for treatment. This is a dietary supplement, and by the same token we have demonstrated that it has an ability to support and maintain glutathione, so it can be used in a wide range of conditions that have low glutathione associated with them. We have a generic website that we maintain that has just descriptions and some research information on these various conditions. My practical experience in the clinic, for example in some individuals with Parkinson's, has been gratifying. If we have a couple of minutes I will tell you a very interesting anecdote about two children with cystic fibrosis. Early in the development of this product these two parents contacted me about their children who were then 18 months and two-and-a-half years. Both of them had documented gene defects causing cystic fibrosis, which means that their cells in the lung and in the GI tract are not able to move glutathione, in the lung, for example, to the extracellular lung fluid layer, which is important for the macrophages in the lung to take up glutathione. So they have a block in the ability to use glutathione across tissues. This gave me one of the first real clues that this product had a real potential because both the children improved, one in the lung function (this child had the typical thick mucus that is seen with CF) and improved over a month's period of time, and this child has remained stable. She unfortunately needs to take the liposomal glutathione on a regular basis (meaning daily), but this has been keeping her lungs clear for over seven years now. And the other child had GI tract presentation, and her growth pattern returned to normal and has continued. So that was a real stimulating factor for me. But as far as observation in the clinic, recently I have seen a few individuals with Parkinson's disease that have responded very nicely. Incidentally, there is some very interesting research showing that you can monitor homocysteine levels in people with Parkinson's disease. What we use in adults for dosing is I always suggest people start low and go slow. My target for support is usually one teaspoon twice a day for the initial phases of support, but I always start low and if they have any kind of chronic condition I may use a serving as low as one quarter teaspoon for a few days and then move up to twice a day, with a progression up to one teaspoon twice a day. There are numerous reasons for this, but if you think of restarting the system, it's kind of like an old car that has been sitting aside for a while. If you go in and turn the key, if the engine starts it may push out a lot of junk, if you will. The same thing can happen as you restore glutathione to a system. You can start pulling toxins from one area and perhaps the liver still needs some time to catch up to all this, so by starting low and going slow you can allow all of these systems to come online simultaneously. With children we use lower dosing, usually about a quarter of a teaspoon (100 milligrams) for every 30 lbs., once or twice a day, again starting with a little lower dose initially and moving up slowly. We've had many gratifying anecdotal observations.

JB: Well, Tim, I really want to applaud you. I think there are several takeaways for me in listening to you. I was very impressed when I had the chance to meet you, and even more impressed in having the chance to have this conversation. First of all, I'm very impressed with the scholarship that you take into your observations and in your practice. Obviously your patients benefit greatly from that level of intellectual

inquiry and the way you commit yourself. Secondly, I think the pursuit of this interesting path over the last—I guess it would be since '96 to 2012, now—of your own intellectual inquiry into this field of glutathione and how that translates into improved patient management is just really remarkable. And then, of course, lastly to actually translate that into a technology and proof of concept with your research that you have collaborated on with these investigators is quite unique in our field. I really want to applaud that. I think if we had more of our field taking this level of commitment of their interest into innovation and discovery we would move this whole field ahead much more rapidly. Thank you, and by the way, what you have shared with us clearly has some significant potential clinical benefit in these multitude of conditions that are associated with altered redox and altered detoxification. My very best of thanks to you, and my strong admiration for what you've accomplished.

FTG: Jeff, you've been an inspiration for me in my research over the years and I really appreciate being able to interact with you and your comments are appreciated a great deal. Thank you.

JB: Thank you, and I wish you the best in 2012 and I'm sure we'll all be checking in as this field moves forward because this is kind of at the cutting edge, I think, of where chronic-related illnesses lie: this inflammation/oxidative stress/toxicity connection. You've given us another point of light into the understanding of it and what to do about it. Thanks a million.

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