**Audio Tape Transcriptions of a Workshop by PAUL CHENEY, M.D.,
on the Clinical Management of Chronic Fatigue Syndrome (CFS) and HIV Infection**

February 5-7 1999 Afternoon workshop using case studies and slides. Paul Cheney, M.D.
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Audio tape #2 Transcript
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"This session is on the clinical management of Chronic Fatigue Syndrome. And I'll go through a series of slides that I think outline a number of key issues and their management, and then go through a treatment paradigm [pyramid actually, I think] that I developed over many years to treat these patients. Then maybe we'll open up to questions.

One of the things that I think is important to know about these people is that they're complicated in the beginning, but I think they become ever more complicated at time goes on. I'm constantly amazed at how complicated the disease is, especially as the years roll by. We'll discuss some of the reasons why. I think they are, interestingly, most approachable from a therapeutic standpoint in the early stages of the illness. But as things go along, they can be more and more difficult. I think there's an end stage to this disease that may not be well treated no matter what you do, and we'll talk a little about what makes those people so treatment resistant.

I'm going to begin by sort of coupling to the talk this morning about this **glutathione defect**. I believe this glutathione deficiency is the key problem particularly over time, and makes the patients very difficult to manage from a detoxification standpoint. Because every time you try to intervene and detoxify when they have this underlying defect, you actually make them quite ill. You can actually put them in the hospital attempting what appears to be a good detox program that works in a lot of people, but will not work in this subset of very sick and treatment-resistant people, which is mostly what I see.

Another little caveat to note is that I don't know if what I'm going to be saying will generalize to all chronic fatigue syndrome. It seems like I have a larger collection of sicker, more treatment-resistant patients. That's kind of what I see. So when people say, "Well I did this-and-so and that-and-so and it worked on everybody and they were well," I never see that. Maybe we're not looking at the same group of people. I think there are milder forms of this disease that may very well respond to all kinds of treatment forms.

The glutathione resistance or glutathione deficiency was first noted when we began measuring whole blood glutathione levels and began to see these **low to low normal glutathione levels**. We were also looking at functional markers of glutathione, such as lipid peroxides. Both blood lipid peroxides and urinary lipid peroxides, which is an endpoint functional indicator of glutathione functionality. We're also seeing other functional indicators of glutathione problems such as citrate elevation and alpha ketogluterate (sp?) depression on organic acid analysis.

What was curious to me was that in many ways we were able to make progress on just about everything that we cared to clinically measure as we applied our therapeutic regimes--we saw a lot of people getting better--we saw a lot of things getting better, except this glutathione. It seemed to be extremely resistant to therapy. It was as if something was hanging on and preventing our ability to change this system. I don't know, and I still don't know to this day, why that is. But whatever is doing this, is a key to this illness, I think.

This is just a slide of the degree and the reality of this glutathione defect. Seen in red on the left, relative to control groups in blue, they sit right at the margins of normal (although you see some that are extremely low). They sit right at the bottom edge of normality. In addition to this, to indicate that yes this is not only a low glutathione functionally important, is the evidence of urinary lipid peroxides, shown on the right, their urinary lipid peroxides are high, almost double that of the normal population.

In addition to this, we saw extremely low serum **Vitamin E** levels. If you had a glutathione defect, you might expect to see defects in holding vitamin E in its reduced state as it's typically cycled with glutathione between its reduced and oxidized states. And, indeed, vitamin E is very

low and it's very treatment-resistant. You can get lots of vitamin E and not have much of an impact which I think again is an aspect of this glutathione deficiency. If you can't recycle vitamin E, whatever you're getting, just gets oxidized. You may also have problems with oxidizing vitamin E in the GI tract.

We also noted some generally low red cell **selenium** values. But they're even lower in white cells, specifically lymphocytes, which I think is interesting in itself. The point being that this selenium defect may actually be compartmentalized. That is, in some areas of the body the selenium level might be OK, but it other areas of the body it might be specifically depleted. I think it's extremely depleted in the white cell. Of course, if you deplete selenium you're going to cream the glutathione functional system. We also got interested in this low selenium from the standpoint of the emergence in **HIV** disease or the discovery of a gene. It's a glutathione-peroxidase encoding gene present in **HIV** which upon rapid cycling consumes large amounts of selenium within the cell where **HIV** resides. This selenium consumption effect can essentially wipe out glutathione synthesis and then produce apoptotic cell death. So the hypothesis is that perhaps the mechanism of CD4 depletion in **HIV** infection may be involved in this selective selenium depletion of cells in which **HIV** sits, and knocking out glutathione is producing apoptotic cell death.

So the fact that we were seeing selenium depletion in lymphocytes which exceeded the selenium depletion in red cells and by other measures suggested there might be some compartmentalized issue involving this glutathione defect which is going to be even more problematic from a treatment standpoint. Because what if the glutathione levels or the selenium levels are OK in some parts of the body and then really depleted in other parts of the body? That makes it very difficult to treat because if you treat for the selenium defect, you might over-treat in one part of the body just to restore another part. And it doesn't even get at the dynamic issues involved. So we thought we were getting closer to the problem or at least why the problem was so treatment-resistant.

To me, this is a most extraordinary paper, published by Anthony Falci, an expert and head of NIAID and our leader in the **HIV** world at NIH. But he's also a glutathione expert. And he showed in this paper, published in PNS in 1991, that glutathione is an impressive anti-viral weapon. Under cell conditions designed to produce log order growth in **HIV**, simply by raising glutathione levels to 15 millisomething (word?), you can wipe out that exponential growth, which is the white line, down to the yellow line, which is the flat line. **You can flat-line HIV growth simply by raising glutathione in-vitro in the cell culture.** Now 15 millisomething (word?) is only three times physiologic. If you raise the physiologic doses, which is 5 millisomething word?), you get an intermediate line--a suppression of HIV, but not a wipeout. By the way, this also applies to other cytokine-induced augmention of **HIV** in cell cultures, such as TNF alpha and IL-6 when injected into cell cultures also augment **HIV** growth, not as well as somethingesters (?) do, but quite nicely. Again 15 ml (?) glutathione wipes out the cytokine effect.

These two issues I thought were very important to me because it meant that chemicals or toxins such as fourbellesters (sp?) can induce endogenous micro-organism replication rate, especially in the presence of glutathione deficiency. And immune-activation states can also induce the activation of endogenous microbes in the presence of glutathione deficiency. And that might explain why in this, quote, immune-activation state that we call Chronic Fatigue Syndrome you see a lot of endogenous viral activation such as EBV, CMV, HHV6, mycoplasma incognitus, chlamydia pneumonia, candida, and on and on and on. You see the activation of this microbial ecology, and why is this happening? It could be that it happens because cytokines in excess stimulate these organisms, especially in the presence of glutathione deficiency. The converse is true, however. In the presence of good glutathione levels, it's very difficult for that to happen.

This is a diagram of what might be going on in the initial stages of this disease, Chronic Fatigue Syndrome. Namely, some virus gets into that person, or activates, which has one of these glutathione-peroxidase encoding genes, producing rapid cycling production of seleno-proteins [selenium-bound proteins]. Those seleno-proteins don't do much functionally, but they consume vast quantities of selenium, anywhere from two to 16 selenium atoms per seleno protein. Upon selenium depletion, you wipe out glutathione synthesis and functionality, resulting in rapid viral replication, redox (?) shift causing energy drops and detoxification failure at the cell level.

If glutathione deficiency drops low enough and redox shift rises high enough, this cell simply dies, an apoptotic death.

[Inaudible question.] I don't know. I don't know what the factors are that govern this. It's just an

important idea. If this is going on, you might expect to see specific compartmentalized selenium deficiency in the cells in which viruses like this sit. Now the cells that propose to cause chronic fatigue syndrome, typically sit in the lymphocyte fraction, such as EBV, HHV6 and so forth, and they would be expected to produce a greater effect of selenium depletion in the white cells than other places.

Conclusions from all of this are: Glutathione has potent anti-viral properties--if you raise the glutathione level you can stop the replication of most any, at least, intracellular pathogen. chronic fatigue syndrome patients are glutathione deficient. Glutathione deficiency itself has a potent pro-viral effect. That is, not only does (high?) glutathione levels tend to act as an anti-viral, but glutathione deficiency produces a pro-viral effect. It can actually augment viral replication. Augment it from the case of toxins, toxins could augment viral replication and also cytokines themselves. So immune-activation states would itself augment these things.

A seleno protein encoding gene would provide a significant survival advantage to any microbial pathogen. What a great gene to have if you're a virus. Because if you have this gene, you can't be killed. And some of the most vicious viruses on the planet--the hemorrhagic fever virus, such as ebola--ebola has this gene in spades. **HIV** has this gene in spades. Hepatitis B and C have this gene. Other viruses are expected to have it. HHV6, strain A, is thought to have it because it's a lytic virus. The most interesting possibility is that this gene can be passed around from virus to virus, especially by retroviruses. Retroviruses have the unique capacity to insert pieces of themselves into the DNA of both human host genomes and also into viral genomes. So **HIV** could actually be spawning new and more virulent virions simply by stashing a gene like this in the next piece of DNA it sees in which it co-habitates. And that's interesting because **HIV**, HHV6 and mycoplasma incognitus all co-habitate and co-infect exactly the same lymphocyte cell linings. Therefore, the opportunity for transmission or sharing of this gene exists.

The reason I mention all of this to begin with is because I'm trying to set the stage for how important it is to address this glutathione defect. It could be THE major issue in this illness. Maybe not so much in the beginning, but over time become the major issue. Because we're dealing with a sub-group of people who have cellular detox failure and all that that causes. Because if you have cell detox failure, you become a canary to your environment. You are vulnerable to the lowest common denominator of the toxin that you happen be be exposed to, or have. If you have mercury in your mouth, you become mercury toxic when you get this glutathione defect. Because a major defense, perhaps the major defense, against mercury toxicity is in fact glutathione. If you have a toxic GI tract--and everyone in this room has a toxic GI tract--portal circulations are intrinsically toxic, they always have been and they always will be. If you get a glutathione defect, then you become vulnerable to your own cell toxicity, specifically the portal circulation.

Of course we can modulate that toxcicity by giving you a bad gut ecology, wiping out your good flora, populate you with some bad flora and make things even worse. But even under the best circumstances, this glutathione defect would make it very difficult to achieve health simply by addressing only gut ecology. Because even normal gut ecology is too toxic when you have this problem. The point is that the glutathione defect is a central issue in any detoxification program. You can't be looking at sources and addressing those when you have detox failure. That's why a lot of CFIDS patients don't do well under a lot of detoxification programs.

What we got interested in... we found out that when you give oral reduced glutathione, it helps a little bit in some people, especially these pressure toxic headaches they get. But when you keep raising the dose, it actually gets sick again, and was never a very impressive response. When we tried **NAC** [N-Acetylcysteine], we saw some evidence of toxcicity. In the use of NAC--I'm concerned about high-dose NAC in this disease. I think it may be toxic. We tried other methods to affect glutathione. Nothing seemed to be working.

Then we got wind of this product [called **Immunocal**]... it's basically undenatured whey protein, lightly denatured to preserve the peptide action of this milk protein. It's concentrated to about 90 percent protein and it's very, very lightly denatured. In fact, the more lightly they denature it, the better the action appears to be. And the more they denature it, the less active it appears to be. In fact, if you denature it completely, down to its constituent amino acids, it really doesn't work well at all. People who normally have milk protein allergy seem to tolerate this, by and large. Not 100 percent, but by and large.

This is the data from a six month study. There were eight people entered into the study, seven of them completed the study. We got data on seven of them. One dropped out at three months

for a reason involved with the design of the study. The first three months of the study we treated with two packets a day, and then the second three months, half were randomized to two packets a day and half were randomized to one packet a day. We wanted to see if you could tell a difference clinically or by other means between one packet a day versus two packets a day.

We did this because there was some indication that the more you treat with this, the higher the dose, the better the effect. This is urinary lipid peroxides combining both the two packs a day for six months, followed by the two packs a day for three months and one pack a day for three months. You can see there's a nice steady drop through six month in urine lipid peroxides, which is an endpoint functional marker of glutathione. When you segment out the two packs a day for six months group, they have a much nicer drop. When you look at the group that goes from two packs a day to one pack a day, you can see this nice dip where they started going back up (in their urine lipid peroxides). Suggesting that one pack a day doesn't work very well.

By the way, you can extend this--there are people, I've discovered since the study was done, that do really well on three packs a day and not very well at all on two. So clearly there is a dose response issue. Two packs a day would probably be my recommended starting dose, but I wouldn't hesitate to go up if if seemed like it wasn't working.

(Explains guy who dropped out of study.) The red line stops because this is a guy who dropped out of study after three months because he had gotten tremendous results from two packs a day. He was randomized to one pack a day and he refused to do it, so he withdrew from study. He said, "I've got something that helps me. Goodbye."

There are 10 grams in a pack. [Someone asks him what his source is.] I'll talk with you later. This is a generic talk. I don't sell anything... I don't mean to sell anything. [But we all know that Dr. Cheney was talking about Immunocal, don't we?]

This is whole blood glutathione. This is interesting. When we looked at whole blood glutathione, there was almost no change. There was a little drop at month two, it was almost like the system got engaged. Glutathione that wasn't being used was suddenly being used and the glutathione stores actually dipped at the second month, and then they started to come up. You can capture that at month three. And at month six it started to come up. But overall not much change in the actual whole blood glutathione. Suggesting to me that it isn't whole blood glutathione status that this is affecting. It's affecting the whole glutathione system.

So what you're not seeing here... it's like you're looking at a whole sink filled with glutathione and you're not seeing the dynamism, the utilization of glutathione. As evidenced by dropping of the urine lipid peroxides. Or yet, there's some other aspects of this product I don't understand. But you can see that this group had borderline glutathione levels. I have a feeling according to other reports that if they had severely depleted [whole blood] glutathione levels, then you see rising glutathione levels, if they're severely depleted. But in these marginal cases, we just didn't see much.

[Question: What about 5 or 10 packets a day?] I'll get to that... it is an interesting idea.

This is the exciting stuff. We wanted to see not only if this product improved glutathione functionality, which it did, but we also wanted to see if it knocked out micro-organisms, like the PNS article said it would. So we measured for IgM (visa?) the inverse dilutions of IgM for chlamydia pneumoniae. Chlamydia pneumoniae is an intracellular pathogen. It's a common cause of hospital-acquired pneumonia. It ubiquitously infects the population, but seems to activate under certain conditions. And if it activates, some of the clinical conditions of this organism are chronic sinusitis, pharyngitis, and laryngitis. But it also gets into the central nervous system.

In a study published by a neurologist out of Vanderbilt showed tha chlyamdia pneumoniae may be a very important pathogen in multiple sclerosis. Indeed, data they shared with me recently (and this is coming to publication soon) showed that 80 percent of the cerebral spinal fluid of MS patients is actively infected with this organism. Versus 15 percent of other neurological diseases that are not MS. In a journal-published article on neurology, aggressive treatment for chlyamdia pneumoniae rapidly reversed an acute exacerbation of multiple sclerosis.

So we measured IgM levels for this pathogen at Vanderbilt. Most laboratory measurements of this organism are not very good, so this is a research grade assessment, and probably may not generalize to the run-of-the-mill types of tests that you might get in your local labs. But IgM

elevations of 1 to 1600 (?) dilutions is evident of significant active infection with this organism. Six months later, it just wiped it out. IgM just fell to normal levels. It didn't really matter whether you were taking one pack a day or two packs a day. Just wiped it out. Makes you wonder what this might do for MS. Think about that.

We also looked at mycoplasma fermentans and mycoplasma penetrans. Both of these pathogens have been linked to Gulf War Syndrome. They've been linked to chronic fatigue syndrome. Again, they may be a relatively ubiquitous mycoplasma species, intracellular, and can cause a variety of problems when active. Again, by PCR done in Irvine, California. We were able to show that this product also wiped out mycoplasma incognitus and penetrans.

By the way, this study was designed to do some microbial testing on everybody, but not everything on everybody. The patients were allowed to pick and choose depending on what we had in their chart before. We weren't able to do everything on everybody because they were paying for this.

Then we looked at HHV6. It was a little mixed here. We tested three people By the way, this study was designed to do some microbial testing on everybody, but not everything on everybody. The patients were allowed to pick and choose depending on what we had in their chart before. We weren't able to do everything on everybody because they were paying for this.

We did HHV6 rapid culture testing, which is a technique developed by a company in Wisconsin. This particular culture technique uses an intermediate (captures fiberglass?) cell line, so that are positive only if you are really infected, so it reduces false positives to zero. That is, uner these conditions, all normal people are negative. You have to do that because HHV, both A and B strains, are relatively ubiquitous. Under these conditions, we had two positives and one negative at beginning of study. The person on two packs a day went to zero culture (negative); the person on one pack a day stayed positive. The person that was negative stayed negative. Suggesting that maybe this isn't as good against viruses as it is against bacteria, but at two packs a day it might be good against viruses. Again, the numbers (of participants) are a bit small.

But to me, the satisfaction of this is tremendous because I'm always faced in this disease population--well, are they sick from EBV? or are they sick from HHV6? or are they sick from mycoplasma incognitus? or are they sick from c pneumoniae? And the [traditional] treatment for mycoplasma and cpneumoniae is 18 months of triple drug antibiotic therapy. And if we're wrong on this issue, we've wiped out their gut flora and leave them a gut ecology cripple for the rest of their lives. So now what we have is a nice way to address almost any micro-organism that happens to be there. [**Using Immunocal.**] Just as the PNS article suggested.

[Someone asks if there is a protocol to give people with **HIV** this product.Cheney responds yes.]

Finally, how did the people feel? Their glutathione functionality improved, though their glutathione levels were marginally improved, and they had significant wipeout of micro-organisms. How did they feel? Five out of six (seven?) felt significantly better. Three of those five thought this was the best thing they had ever tried. They said it was tremendous. In fact one dropped out of the study because he refused to stay on the protocol at only one pack a day.

There were a couple of non-responders. But you'll notice that the two packs a day were the best responders. There is a differential issue still imbedded in this--namely the dose. The dose might need to be upped to see maximum benefit in certain individual cases.

They're continuing to do well.

I guess I should give you some caveats about what these patients said.There's a woman in Manhattan and she said for the first time since she's had this illness, she had a sense of well-being. As opposed to feeling ill.She felt that was her major benefit. We classified her as a good responder.

We had a mother-daughter pair. The daughter had Multiple Chemical Sensitivities--wore a mask everywhere, was wheelchaired around, very sick, bedridden, essentially taken care of by her parents, fed and bathed and dressed. Anyway, she probably had the very best response. Her Multiple Chemical Sensitivities disappeared. And she's now walking around and thinking about going back to school and, at last report, she's doing extremely well. She was probably the sickest. Her mother was not nearly as sick as she was... her mother had a significant

improvement in energy and is doing very well too.

We had a man who was a businessman in Charlotte. Every time he pushed himself, he crashed. He could do some things, but every time he went past his boundaries, he crashed. He stopped doing this [on Immunocal]. And then we had an attorney in San Francisco who felt a little better energy. Could tell she was on the product, but nothing to write home about. Would classify her as a fair responder.

Then we had a couple of non-responders. Interestingly, these two non-responders were NOT the sickest. They were probably the wellest of the seven. I have some serious doubts about their compliance with this. It was very difficult to assess them because they were both working and there were a lot of things going on in their work and it was hard to assess them. Neither of them could tell much difference.

[Question: Did you provide other supplements?] Yes, I did. But these were not new patients. These were patients who had been in my practice and were on a stable program. I'll tell you what they were on in a minute.

This slide is the most important slide I'll present. This slide is a description of the three phases of chronic fatigue syndrome. We had been a little bit suspicious that this disease isn't the same thing in the beginning as it is in the middle and in the end. It's not the same... it kind of changes. We had sensed this as physicians, but we typically thought that, well, their disease is going along. They're aging, or other factors. But now we think we know why they shift in these three phases. It's important to recognize these three phases, because each phase has to be dealt with differently. We kind of went from a vague feeling that the disease evolved to more certainty that it evolved, having to do with the discovery of one important item, and then the appearance of phase 3 in large numbers, which is only now beginning to arrive in my clinic.

First, the discovery was R-Nase L activity. R-Nase L activity is that anti-viral enzyme that I mentioned, may be a key, especially in the early phases of this disease, that ampligen regulates, or downregulates.This R-Nase L activity was seen significantly elevated primarily in the first five years of illness. After five years, there's a progressive loss of this enzymatic upregulation. Such that by phase 3 you don't see it at all anymore. So if you measure R-Nase cell activity across the whole spectrum of this disease, you'll see it high in some patients and normal, or zero, in some patients. Making it not an ideal test for diagnosis of chronic fatigue syndrome because it's not sensitive enough to the disease. Although it may be very specific for it. There was that observation.

And secondly, we began to see larger and larger numbers of phase 3 illness. Phase 3 illness. This is what they sound like: "Dr. Cheney, I've had this disease for about 10 years and, if it weren't for the fact that I can't do anything, I would think I had recovered." They essentially say, "Within my boundaries I have very little suffering anymore. I don't suffer any more. I have no significant symptoms any more. It's only when I exceed these boundaries that the symptoms come back and I get sick again." So my problem now is not a person who suffers but a person who cannot do anything--or do anything like I used to. I'm seeing more and more and more people like this. And I think that 10 years ago I didn't see anyone like this, that I recall. Or maybe they didn't show up because they didn't think they were sick anymore. That's phase 3.

I took a vector approach. Namely an x axis, which is the "Misery" axis. And a Y axis, which is the "I'm Limited axis." I suggest to you that this disease marches along. In the beginning, it's more of a misery disease in which they complain bitterly about three primary symptoms: I have no energy; my brain is shot; and I hurt. That's the misery phase. Amazingly, some of those people function pretty well in the beginning--or they try to function in the beginning, and maybe they manage to and maybe they don't. And if they don't function they blame it on all those terrible symptoms they're having. That's phase 1.

Then they move along to Phase 2. That's marked by a significant down-regulation of R-Nase L. Therefore they don't have that underlying protein synthesis disruption that R-Nase produces. Their misery lightens up a little. But at the same time they notice that they can't even do as much as they did when they were sicker. They're more limited and they're still pretty sick.

In Phase 3, they have no R-Nase activity and symptomatically they're better, they're much better, but now they're really locked in to their boundaries. So we think what's causing this limitation is the end damage that's done to deep brain structures, particularly the hypothalamic region and the loss of dynamic hormone responses necessary to meet the exigencies of life. So

they're essentially locked in to a functional bubble. And damage done to mitochondrial DNA, which I suspect is substantial.

Now that doesn't mean this endpoint is totally fixed. I think there is a good bit of plasticity to the central nervous system and I think there can be significant resuscitation of brain function even in a phase 3. I also think the mitochondria might not be completely lost. But the loss of mitochondria--putting an energy ceiling on them--and most importantly, loss of dynamic hormone response, is what causes this limitation. And that is the endpoint of this disease.

[Inaudible question.] Yes, not only low cortisol levels, but more importantly, low dynamic response to any stressor. In other words, it's not just that the cortisol static level is low, is below normal, but when you stress them out, rather than doubling or tripling the level, they go in reverse. It's this dynamic loss that is going to be so limiting. And that's a hypothalamic injury, I believe.

Now what's toxicity doing? Well, of course R-Nase activity knocks out detox systems, so now you start getting toxic. The feature of Phase 2 illness, I believe, is primarily toxicity issues. So phase 1, the issue is R-Nase cell. Phase 2, the issue is toxicity and therefore toxicity, detox support and source toxicity is the focus. Phase 3, it's resuscitation of the brain and to some extent mitochondrial DNA. I think there are different phases of the illness and you have to approach these phases somewhat differently.

Now, treatment. This is a treatment pyramid. The bottom is the most important. It's the most difficult to get people to do, but I think it's probably the most important part of it. Limit setting. These patients are very susceptible to push-crash phenomena and they need to learn to stay within certain boundaries. To the extent they do that, they tend to do better. To the extent they don't do that, they will not do well.

**Elimination diet**. The more I get into the issue of diet and food sensitivities, it's obvious to me that the single most common antigen to which we are exposed is food proteins. If food protein is not properly digested, it's a significant inducer of immune activation in the gut, and it can maintain this disease indefinitely. Put another way, as long as you eat, you cannot get well, with chronic fatigue syndrome. So ultimately you have to begin a process of determining the foods to which they are reacting, and eliminating those, and going more progressively to an oligogenic diets. Perhaps more importantly, is to digest the food in the first place, which I don't think they do very well. They then get undigested food protein coursing through the small bowel. There are permeability issues that affect the gut. If the gut is permeable, nothing digests completely. If it's permeable, the undigested food antigens course across the boundary and get exposed to immune competent cells and then you're off to the races with this disease. So I think a lot of attention to elimination diets, and improving digestion and gut epithelial function can pay huge dividends in this patient population. I've seen people in 30 days have huge clinical responses simply by this very simplest of moves.

**Rebound exercise**. This was studied by NASA in the 1970s in regard to astronauts returning to earth from low-earth orbit. After six months in orbit, you lose your autonomic nervous system capacity to stand in a gravitational field. You simply faint and seize. If you remember these astronauts, when they took them out of the capsule they had to drag them out vertically because they would faint on standing. They end up with a disautonomic condition similar to chronic fatigue syndrome patients. NASA figured out that the best way to bring back the autonomic nerve system was to bounce. So they put them in these bungee cord contraptions and they just bounced them--this up and down motion sets a sinosotal (?) input into the brain and essentially regulates autonomic tone and improves the, quote, autonomic nervous system. Rebound exercise is the best form of exercise for these patients. It's very easy, it's non-weight bearing, it does a very important job I think in autonomic tone in a population that has difficulty with exercise. You can add in arms, legs and abdominal motion while bouncing, to tolerance. The most important thing about exercise is to not have them do aerobic exercise. I even believe progressive aerobic exercise, especially in Phase 1 disease--particularly in Phase 1 but possibly in the other phases--is counter-productive. And when they get better they're able to do progressive aerobic excercise, but that should not be the focus in the beginning.

**Stress managment**. They have a defect in the HPA axis, in response to stress, so they hae to be stress limited. The need to learn how to handle stress better, and there's all kinds of ways to do that.

**Belief systems**. There's an over-representation of Type A patients in this disease. Their

personality types are very bad for them when they have this disease at the same time. They have to change their belief system. A change in orientation from "doing" as a definition of themselves to "being" as the definition of themselves. And to orient from recovery to healing. People can heal although they may not recover. And people can "be" although they not "do." As soon as they orient toward "being" and healing, interestingly they are far better able to "do," and I think far better able to heal--and recover. It's almost as if once they turn away from their goal, and march off in a different direction, they actually have a better chance of getting back to the goal they turned away from. Conversely, if they're going to "do" no matter what and recovery is the absolute goal for this, I don't think they do that well.

[inaudible question] I think they have a defect in mitochondrial function. And if you push the mitochondria and it's defective you kill the DNA. So it's a short way to lose your DNA. This pyramid is an integrated program. No one element suffices--it's everything working together. It's a stepwise program, meaning you move up the scale every one or two weeks. You don't start it all at once. Patience is required. I find that people who inaugurate such integrated programs may not espond very well for many, many months. And finally, this failure that occurs... and it's very important I believe to analyze why these kinds of integrated programs fail. And I think one very good reason to fail is R-Nase activity. If the 37 KDA protein is very, very active, it has six times the digestive ability of the normal 80 kilodalton (?) protein. It's sitting there chewing up the messenger RNA encoding for every enzyme in their body. As long as that enzyme is cooking, I don't think you can make much progress. And it could be a very good reason to fail.

**Non-compliance**. Sometimes patients don't do what you tell them. Or I missed something. It's not usually something I didn't think of. It's usually something I thought of, but dismissed as probably secondary. Among those include, "Well, the cavitation probably isn't the reason." Or, "The root canal tooth is probably not the problem." And in fact, it was the problem. Sometimes revisiting those issues down the road if you get a failure is very good way to recoup some progress.

It's not time yet. I think this disease is going to pass through all three phases: phase 1, phase 2 , phase 3. And sometimes they haven't gone through all three phases yet. And I think some people don't respond because their disease is by and large over and what you're dealing with is residual injury to vital brain structures and mitochondrial DNA, and therefore the focus needs to shift more to that rather than traditional therapies for chronic fatigue syndrome.

**Neural protection**. This is very important, especially in Phase 1, but also throughout Phase 2. These brains are being injured. I believe they're being injured by xenobiotic toxicity. They could be injured by viral invasion, particularly HHV6. They could be injured by chlamydia pneumoniae. Any number of possibilities. And so I think it's important to protect the brain. Because in the end, if you don't do this and you get to Phase 3, there won't be a brain left, or I think there will be significant damage, and that damage may reveal itself when they get a lot older. Magnesium is an important element. They are magnesium depleted. Depleted magnesium inaugurates excessive neuronal firing rates. The threshold potentials drop, and these neurons are firing, and you undergo in effect neurotoxicicity due to excessive NMDA firing based on magnesium depletion.

I always like parenteral--it always works best. I give it every night. One cc every night or two cc's hree times a week. But sometimes the magnesium sulfate is hypertonic, it's caustic, they get tissue maceration over time. So it's something you can't do in every person, they won't tolerate it. So we use the glycinates which we think are the best for this particular issue.

**Klonopin** is my most effective drug over the years. It's a benzodiazepine, long acting. Indirectly agonizes the GABA receptor and blocks NMDA associated neural toxicity. We use very low doses in the daytime. We find that if you give a low enough dose they actually get a lot clearer and think better in the morning. If you exceed that dose, they get drowsy. But when you get to the right dose in the morning they think better. I think it has to do with resetting this neuronal threshold potential along a continuum. And at night we use higher doses.

**Doxepin elixir**. An antidepressant with POTENT anti-histaminic properties. I suspect that this is the most powerful antihistamine known to man and it gets into the central nervous system. We use very small amounts of this. I think it's adjusting the histamine receptors, which are the grand maestro of the central nervous system, and downregulates it, which is beneficial. Small doses at night.

**Taurine**. Taurine is very important in brain protection. It's kind of interesting--cats that don't eat

taurine go blind. They can't make taurine, they can only eat it. It's only found in meat. If you put cats on a vegetarian diet, they go blind, because taurine is essential for retinal function, and the retina's just dies in the absence of taurine. Taurine could be an important issue in some of these patients.

**Neurontin**. We've been using Neurontin sparingly. Neurontin could be a very potent weapon in resistant cases, but I'm a little bit concerned about the extremely high doses that are being used in some patients.

**Mitochondrial DNA protection**. In addition to protecting the brain, I think mitochondria deserve a considerable amount of protection. Otherwise there may not be any at the end. We use a mix of things--multi-vitamin chelated mineral complex.

**Plant bioflavonoids** are very important. We showed some years ago that if you just use multi vitamins, you don't get much improvement in lipid peroxidation until you add in the plant bioflavonoids, which I think act to couple, oxidize and reduce states of these vitamins. Otherwise, they don't work very well. Examples of plant bioflavonoids are **proanthocyanadins, pycnogenol, silymarin, quercetin**, and there are many others..

**CoQ10** is a critical item in protection of the DNA. We use a lot of it. I think the more the better, but realistically 200 mg. We tend to use it crunched under the tongue since it's not very well absorbed, although there are other absorbable forms that can be swallowed.

**Lipoic acid** may be one of the most important of all of these, in high doses, particularly for the central nervous system.

Extra **vitamin E** because they're vitamin E depleted.

And melatonin may be helpful also. It's a potent antioxidant in the brain, particularly.

**Detoxification**. This needs to be individualized. Everyone has a more or less unique source of toxicity issues. One thing I always give is high doses of **B-12**. I never knew till I read an article in a British medical journal that B-12, at least in **hydroxycobalmine** form, is a wonderful detoxification agent. It's used in high doses to treat cyanide poisoning because it binds to cyanide and removes it or detoxifies it. When you're using B-12 as a detoxifier you have to use very high doses--at least as many B-12 molecules as there are toxins. It's brain specific. And in chronic fatigue syndrome patients two thirds of them have no detectable B-12 in their brains. Even though their blood levels are normal.

This is work out of Sweden--assays of cerebral spinal fluid show that two thirds of cases have detectable B-12 in the brain even though the blood levels are normal. So B-12 is highly compartmentalized, and it could be normal in the blood and absent in the brain. It is absent in the brain I believe because it is being coupled by toxins--neurotoxins, probably xenobiotics--because B-12 couples to nitrogen. Nitrogenous waste molecules in the brain are coupling out the B-12 as fast as it's leaking in, and they end up with zippo B-12 in the brain. So you have to more than replace that. We use high doses.

We do not recommend **cyanocobalamin** because cyanide coupled to cobalamin is not the thing you want to use to detoxify people. To the extent that it might be a good detoxifier, which it isn't, you just trade cyanide for the toxin it removes. We prefer **hydroxycobalamin**, and perhaps **methylcobalamin**.

[Question: Do you have to worry about **folate** deficiency?] We give folate, significant amounts of folate orally, anyway, so we don't worry about that.

**Root canal extraction**, and particularly careful regarding bone excavation--this could be a big issue in some people. And here electrodermal conductance (?) might be the single best, and perhaps muscle testing as well--may be be good methodologies for identifying those people with toxic root canals, an extremely toxic source, and may have to be removed or you may not make progress anyplace else. Jaw cavitations, for the same reason may need to be addressed some people. Heavy metal issues could be very prominent in some people. Here, though, we have to be careful in these detoxification approaches. If they're glutathione deficient and you mobilize mercury in an aggressive mercury detox program--I have seen a lot of people where it seems as if they get a lot worse. It's almost as though they're loading mercury into the brain and are suffering extensive injury from that. So I believe that I would hold off on heavy-duty detoxification

until I supported the detox system. Particularly with glutathione. **DMSA**, as a chelating agent, is the one I've seen the most trouble with. Some of these patients are put on very aggressive programs, so they're on different kinds of dose regimes. But I still think that while it's important to get rid of heavy metals, most of them are too vulnerable to do so until the glutathione system is improved.

**Chemical detoxification**--some of these people are loaded with all kinds of pesticides and things and they may need to be detoxified ultimately to see success. And again, you'll notice if you just focus on source toxicity and you leave alone the detox issues, which is significant in this disease, I think you actually create problems by mobilizing these toxins that are stored in deep tissues. And then you mobilize them and you end up socking more vital tissues because they are very vulnerable people.

**The "3-R" program** to bring back gut ecology. The remove phase--these are some of the things that I use. This is a highly variable area, and I still haven't figured out the sequence and the best things to use. I seem to be... There's a learning curve for this and it takes many years, but the process is always the same. Remove the bad guys; support and repair the epithelial integrity, and then replace with friendlies. I think the last one is the one you have to be careful about. If they have significant permeability defects and leaky guts and I think giving them 10 billion friendly bacteria with fructo oligosaccharides is a bit like throwing fertilizer on a wheat patch and wondering why things get worse. So that's the last thing I would do.

Liver-gut resuscitation. Again, the undenatured whey protein concentrate, I think, is the most important element. Silymarin, to recycle glutathione between it's reduced and oxidized states. The "3-R" program, and there are some special configured (?) nutrition programs developed by Jeff Bland and others that I think work pretty well in some cases.

[Inaudible question.] Grapefruit seed extract.

Brain resuscitation. Now this, to me, is the exciting area of new interventions in chronic fatigue syndrome. And that's... In the end, you have to bring back the brain. In the beginning the R-Nase L activity, that's a big issue, but in the end it's downregulated anyway and it's out of the picture. And in the end, you may detoxify these people successfully, but they may be left with defects in dynamic hypothalamic control, particularly of the dynamic hormones, such as cortisol and growth hormone. Cortisol and growth hormone are the most dynamic, and of course female hormones are also quite dynamic. So you have to bring back the brain, and I think the answer to bringing back the brain will be the same way that nature brings back the brain. The brain is brought back by peptide and polypeptide action. And there's a lot of very interesting research out there on growth factors specific to the brain. Peptide action in food itself on receptor sites within the brain--they are augment the healing response and they help to resuscitate the injured brain and improve brain, quote, plasticity, end quote. Di ter (?) peptides may be important in this, brain map (?) and fetal bovine growth factors may be important in this. Eventually we'll have recombinant nerve growth factors available. Some are in testing stages now. But I think this is where we'll be going in stage 3 illness, is bringing back this injured brain. Because if we don't do that, they may be over the miser stage but they'll be locked into pretty significant functional impairment. There'll be things they'll never be able to do again.

And finally, a miscellaneous slide, all kinds of other things to do, individualized of course, and range from EFA sources to neurotropics to hormones, although I think hormone therapy needs to be done very cautiously, because typically hormones only further downregulate hypothalamic function, and hypothalamic dysfunction is the major problem anyway. Immune modulation with a variety of agents, and antiviral approaches with a variety of agents.

Thank you.

[Question asked.] The best way to enhance **growth hormone production** is stage 4 sleep. It's not easy. I think stage 4 sleep is significantly impaired in this disease."

---end of transcript---