Sarcoidosis and Tuberculosis—insights from an immunostimulative therapy

PRESENTED BY PROFESSOR TREVOR G MARSHALL
Autoimmunity Research Foundation, CA, USA
Murdoch University, Western Australia

1st Congress of the National TB Association,
St Petersburg, Russia. October 18-20, 2012.

Transcript of http://youtu.be/E2QzPVKtEr0 video.

Transcript

Moderator:

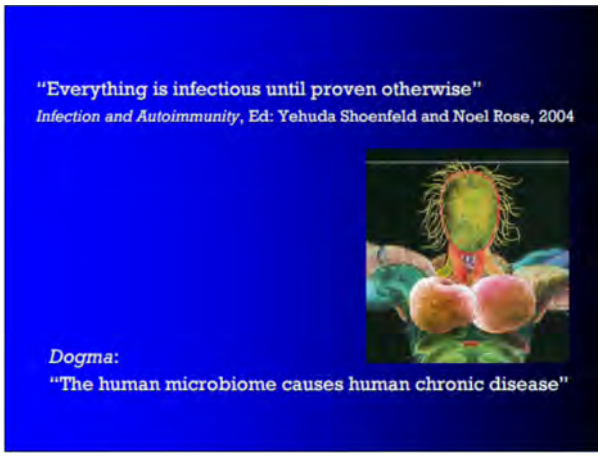
Professor Trevor Marshall, you are welcome for the first presentation. You have 20 minutes.

00:20

Dr Marshall:

Thank you Leonid. OK, this is going to be interesting.

I am going to talk about Sarcoidosis and *Mycobacterium tuberculosis* and what we have discovered from a number of years now, nearly a decade of use of an immunostimmulary therapy, in Sarcoidosis.



00:49

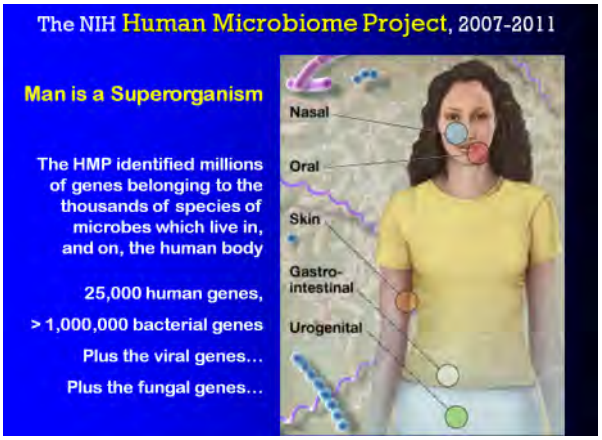
I start with a quotation from Professors Yehuda Shoenfeld and Noel Rose, both very eminent and well known immunologists, who in 2004 made the observation in a book called "Infection and Autoimmunity," that everything is infectious until proven otherwise.

That is a pretty bold statement. Now I am going to extend that in 2012. We can say that "The human microbiome causes human chronic disease, and predisposes for much infectious disease." That is what I am going to be talking about today.

01:28

I will offer no less than the eminent medical journal, *The Economist*, as part of the hypothesis here <humor>. *The Economist* carried in August [2012] the very, very good article "Microbes maketh man," talking specifically about the microbiome and the various diseases which are already being linked causally to the microbiome.

I wanted to point out to you what a wonderful illustration has been used here by the artist that drew the front cover image. You will see that a few times in my presentation.

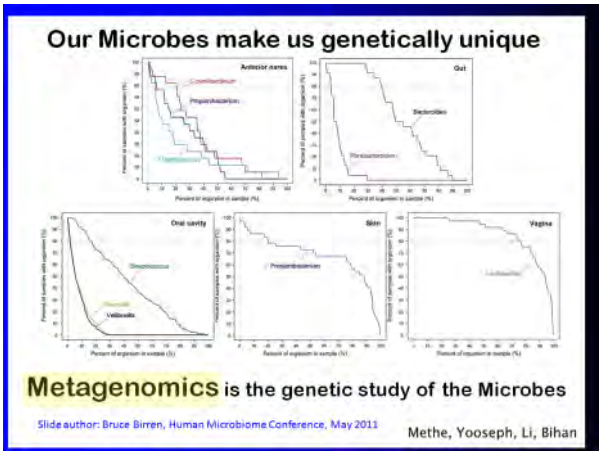


02:15

But if you want something a little more austere, we will talk about the National Institute of Health (NIH) Human Microbiome Project (HMP), which ran from 2007 to 2011. It is finished now, and what they found was that man is a super-organism.

The HMP identified millions of genes—millions of genes—belonging to the thousands of species of microbes which live in and on a healthy human body.

So, for the 25,000 human genes that fundamentally control our existence, there are greater than a million bacterial genes, plus a whole stack of viral genes, and also the fungal genes, and of course, the phage genes.



02:57

That is, it is our microbes that make us genetically unique.

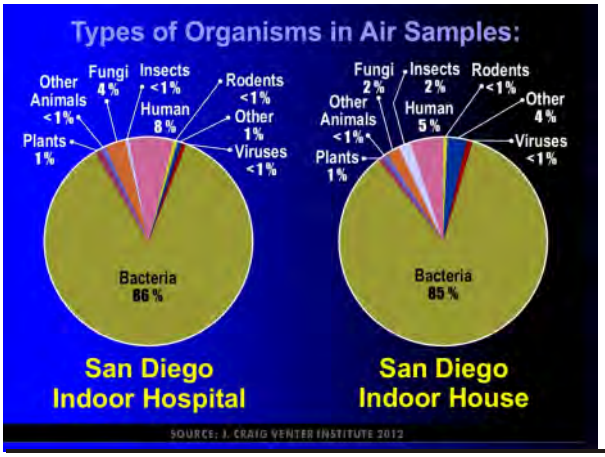
There is more difference between the microbiome of everybody sitting in this audience than there is between the genome of everybody sitting in this audience. Our microbes make us genetically unique.

Metagenomics—meta-genomics—is the study of those microbes.

03:20

So where do you get the microbes from? Well, firstly, you get them from your mother. And at birth, babies are born "dirty" with a gut full of bacteria.

Then very quickly pick more up within the first couple of weeks of life. They will pick up most of the microbes of the extended family. Some very good work has been done by Dave Relman's group at Stanford on that era of life.



03:48

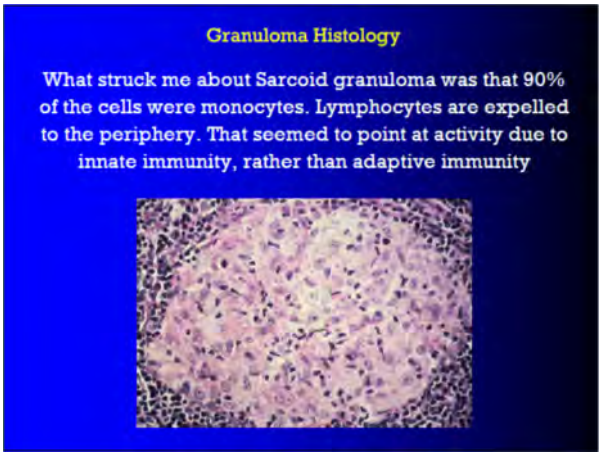
Then you really cannot avoid them from that point onward. If you test the air, which we all breathe—we cannot avoid it—and you sequence the organisms, the DNA which you find in air, well, in a hospital you would expect, maybe in a hospital, that you would find a large percentage of bacteria, about 86%, in addition to human DNA, fungal, and animal DNA, plants and viral DNA. But a huge contribution from bacteria, much greater than the human DNA that is floating in and around a hospital.

It is surprising that you find a very similar thing in the house. Inside a standard house in San Diego, Craig Venter from the Craig

Venter Institute found that once again the air was... about 85% of the DNA in the air was due to bacterial DNA.

04:46

You also pick up bacteria from travel, and particularly from international transport of foods. Over the last five decades our food has become an internationalized commodity. And with it, it brings the microbiome of the region from where the food comes.



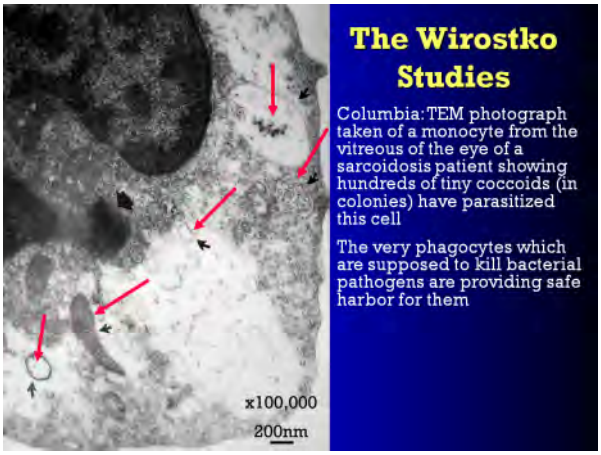
05:04

So a decade ago, I was looking at Sarcoidosis and looking at Sarcoid granuloma, and something hit me about this Sarcoid granuloma.

I noticed that most of the lymphocytes—which are the black stained cells, of course—most of the lymphocytes were around the periphery of the granuloma as if they were expelled to the periphery and not a key part of the process that formed the granuloma.

About 90% of the cells in the granuloma are monocytes and macrophages, but particularly monocytes.

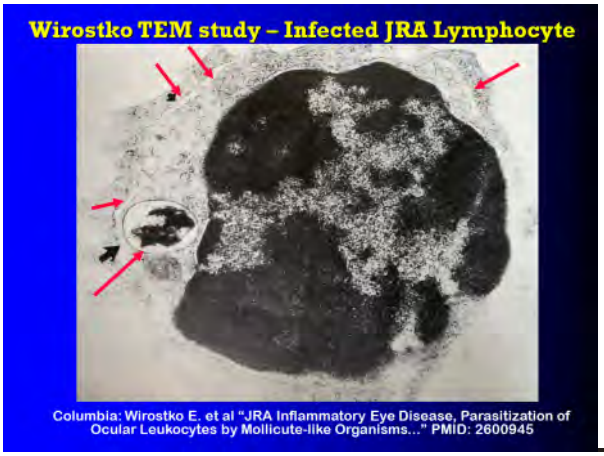
And you know that seemed to point, to me, that the innate activity, the protection within the cells, was likely to be key in a granuloma formation, rather than adaptive immunity—the T cells and the B cells as everybody was suspecting at that time.



06:02

Well, there was a very elegant study done by Wirostko, Emil Wirostko's group, at Columbia University in the 1980's. They used electron microscopy to look at the cyptoplasm of cells—the cells of the immune system.

This [slide] is a monocyte taken from the eye of a Sarcoidosis patient. And you can see hundreds of tiny coccoids which stained—they used a urinal acitate stain for nuclear material—and found that there were many colonies of microbes in the cytoplasm of the cells of the immune system.



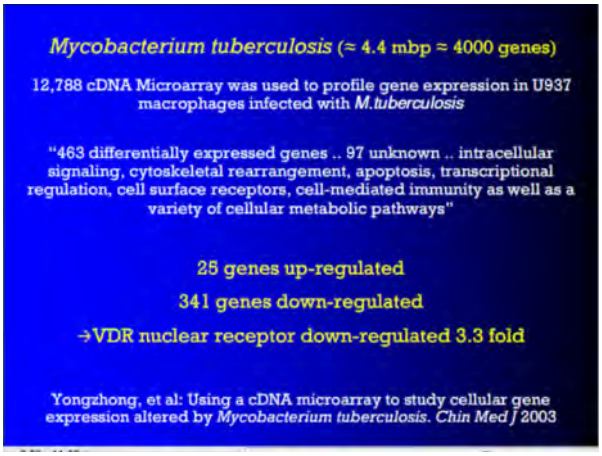
The very cells, the monocytes that are supposed to kill pathogens, were being parasitized and providing safe harbor for pathogens.

06:54

The same thing happens to Lymphocytes. This is from a Juvenile Rhumatoid Arthritis patient, with a large cluster there, looking something like ... a linear cluster there, with linear DNA segments as well.

.

.



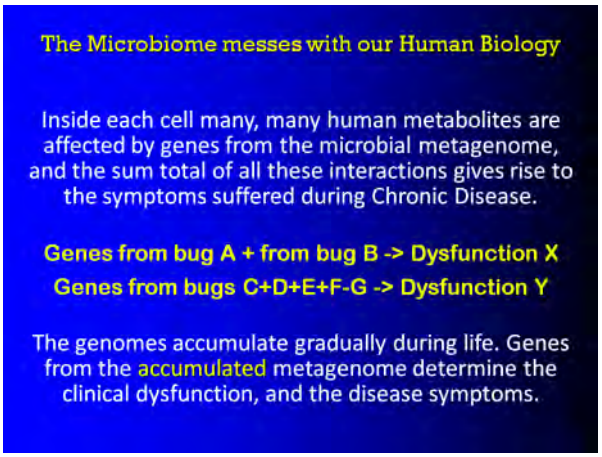
07:35

What happens when pathogens manage to get inside a cell? Well, that has been studied.

In China, in 2003, a DNA microarray was used to study an infection of a macrophage by *Mycobacterium tuberculosis.* What was found was a tremendous change in the operation of the cell.

There were 25 genes up-regulated; 341 genes down-regulated; and the VDR [NR1I1] nuclear receptor, which is the one that we have found is the focus of disease activity in Sarcoidosis, was down-regulated 3.3 fold by the infection of *Mycobacterium tuberculosis.*

In other words, once a pathogen gets inside the cells of the immune system, it changes the way that the immune system works.



08:36

The Microbiome messes with our own human biology.

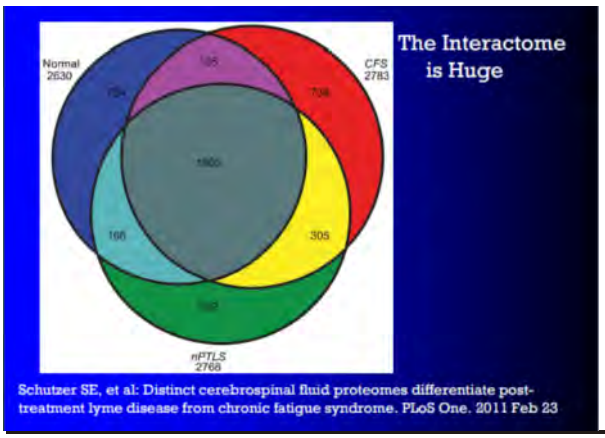
Inside the cell many, many metabolites are affected by genes from the microbial metagenome and the sum total of all these interactions gives rise to the symptoms which are suffered during chronic disease.

The sum total: we are not talking about one or two symptoms, we are talking about thousands of symptoms.

The genes from microbe A and genes from microbe B might lead to a particular dysfunction which I will call X.

Wheras genes from a number of other microbes [C+D+E+F] combine their dysfunction which I will call Y.

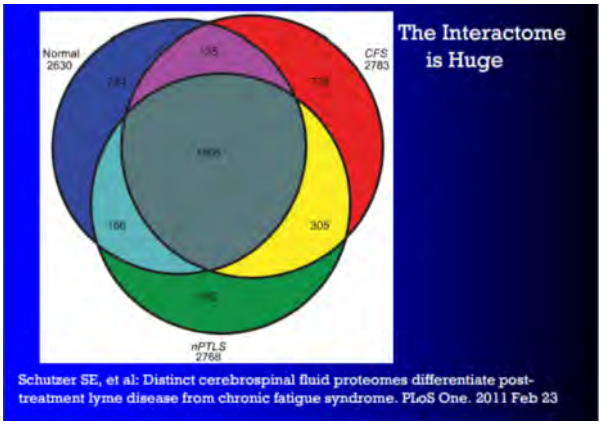
The genomes in the microbiome accumulate gradually during life. We are born with some but we pick them up gradually, based on our environment. Genes from the accumulated metagenome determine the clinical dysfunction, and therefore, the disease symptoms.



09:34

The Interactome is huge. The Interactome is a name given for all the interactions within a cell. When we look at those that are involved in disease, it is absolutely huge.

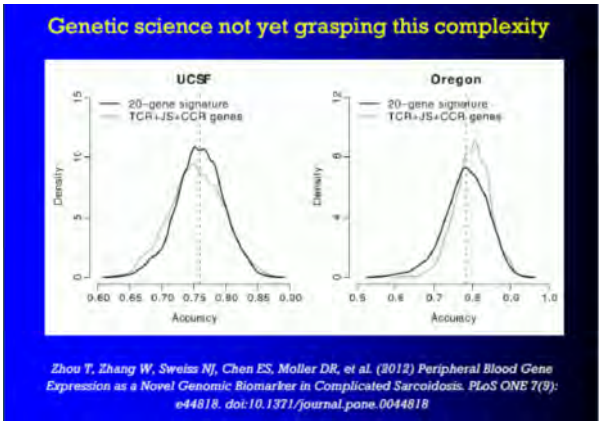
This is a study which was just performed on CSF from Chronic Fatigue Syndrome patients here [next to red], Chronic Lyme Disease, TPLDS, patients here [next to green], and healthy controls up there [next to dark blue].



Out of about 2783 total proteins measured in CSF, a similar number for healthy controls and PTLDS, these were absolutely unique to each of the disease processes:

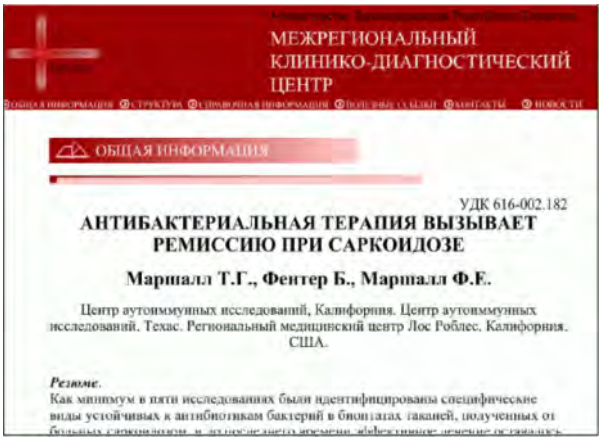
For healthy human beings, there were 724 proteins [dark blue] that were not found in either CFS or PTLDS. In PTLDS, there were 692 found that were unique [green] and in CFS found, there were 738 that were unique [red].

We are not talking about a single [intracellular interaction] pathway here. We are not talking about something simple like JAK-STAT that we can knock out. We are talking about an incredibly complex set of interactions which lead to these incredibly complex diseases we call chronic disease.



10:54

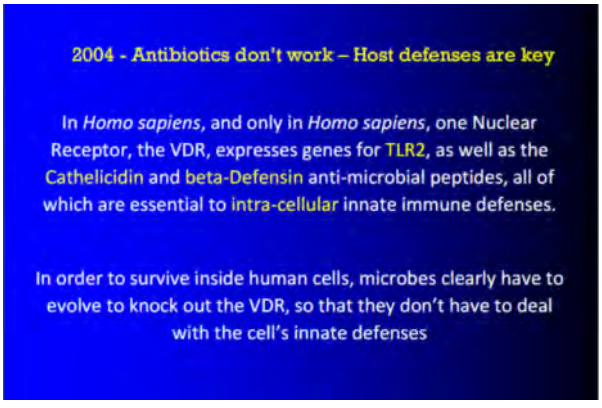
And of course, genetic science is still struggling with that complexity. This is a paper published just last week trying to differentiate healthy controls from Sarcoidosis patients, with about an 80% accuracy, which—they used 20 genes—which clearly is not nearly enough. We are talking about hundreds of thousands of total genes.



11:19

So back in 2004, professor Alexandre Vizel translated one of our papers for the Kazan medical journal. As you can see, it says that antibiotics were effective in causing remission in Sarcoidosis.

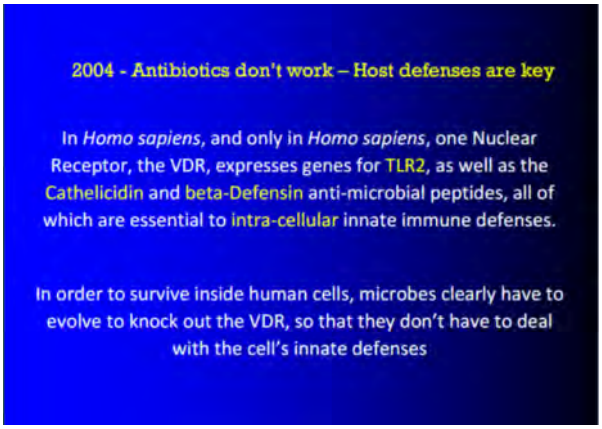
Well, that is not exactly true. We were wrong.



11:49

The patients were, in fact, being given antibiotics but they were also being given a drug for palliation—a drug called olmesartan for palliation. And in the years which have followed 2004, in the last decade almost, we found that the thing that did all the work—the key thing to knocking down the microbiome, the key element or strengthening the innate immune activity so the innate immunity of the idividual can attack the microbiome.

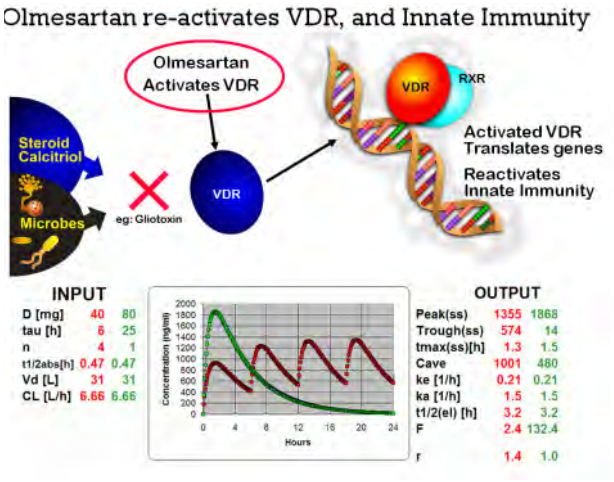
The antibiotics are relatively ineffective and we dropped them about four years ago.



The other thing that is very interesting that this is unique. The way that the innate immune system works is unique to *Homo sapiens*.

Because only in *Homo sapiens* is one nuclear receptor which expresses genes for TLR2, which is a key defense for the cytoplasmic region if the cell—as well as Cathelicidin and beta Defensin anti-miocrobials—all of which are associated and essential to intra-cellular innate immune defenses.

In order to survive within human cells, microbes clearly have to knock out the VDR. Microbes cannot exist in the presence of Cathelicidins. They are very, very effective anti-microbials. The beta Defensins are also very effective and TLR2 is a key signalling receptor. So in order to survive, they [microbes] have to knock out the VDR. That understanding is key to the next step.



13:31
The next step is to find a drug which actually activates the VDR.

What we found was the drug that we were using back when we published the article from Kazan, we were using this drug as a palliative, because it was designed to knock out the angiotensin-II, type 1 receptor, the angiotensin receptor. It is a sartan and it was designed to reduce blood pressure.

But if you change the dosing a little — if you change the dosing so that instead of giving one dose a day—shown by the green pulse on the graph—we give multiple pulses at four to six hour intervals, you can see we build up a basal level of concentration in the bloodstream.

And that changes the operation of the drug. At that point, it starts to activate the VDR.

That is important because in normal, healthy idividuals, the endogenous steroid calcitriol will activate the VDR and that will then cause gene transcription of at least a thousand genes that the VDR is totally responsible for.

But when the microbes come along, they produce toxins. I mentioned gliotoxin and we will see that in a later slide. Gliotoxin is one of the identified toxins that knocks out the VDR, stops it from being activated, stops the endogenous steroid from activating it.

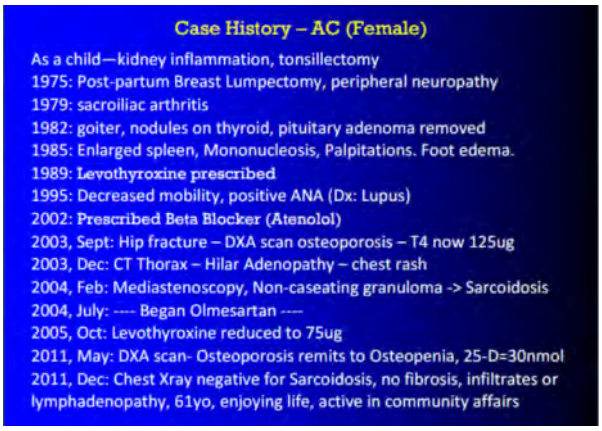
15:07
Once we applied that to a human cohort, we got some amazing results.

This is one of my colleagues from the Autoimmunity Congress in Asia last year [2011], and the key that was really interesting was the coupling of cognitive and memory difficulties with the primary condition, the Sarcoidosis. As the Sarcoidosis disappeared, so did the cognitive and memory difficulties.

15:36

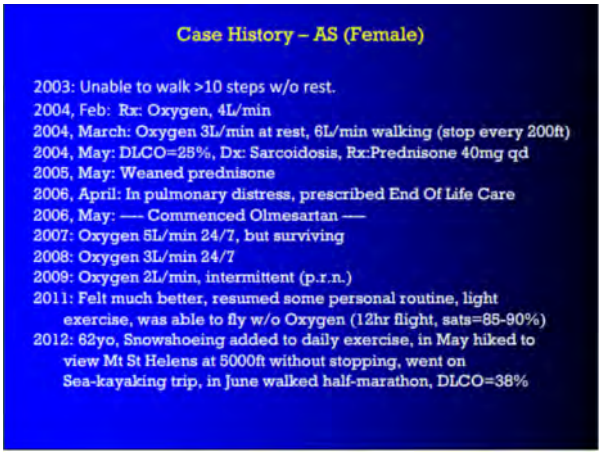
Now I have three quick case histories here. All three of them were pretty sick individuals.

This is a male, born in 1939 with Ricketts. He is now 72 years old. [He] had two various problems and then ended up with two quadruple bypass surgeries, plus echocardiogram version and also had a pacemaker implanted. Then [he] was really sick and about 2004 had a 2400ml pleural effusion. But after beginning olmesartan you will see that there are very few entries. The patient is doing very well. No oxygen anymore. No Sarcoidosis remains clinically at this point. The patient is enjoying life.



16:34

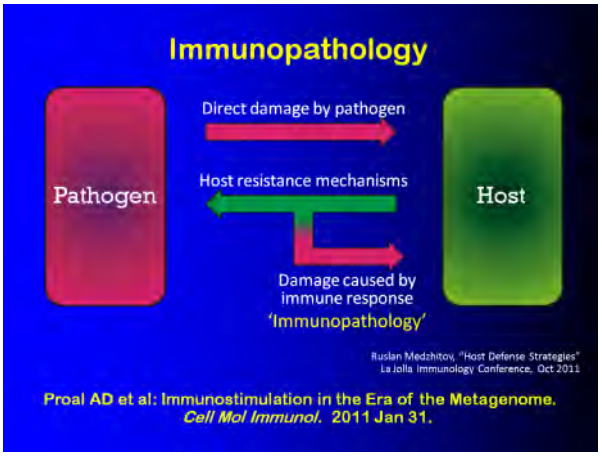
This is a female, AC, who as a child had various problems; tonsillectomy, kidney inflammation, breast lumpectomy post partum, goiter, enlarged spleen and once she began olmesartan in about 2005, over the six years intervening, has basically cleared and is now active in community affairs and enjoying life again at 61 years old.



17:06

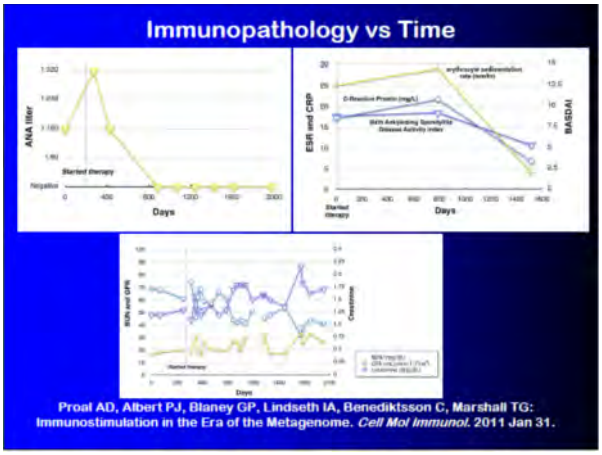
This is a case history of somebody who lives in Alaska. Was on oxygen—very seriously on oxygen—was prescribed end of life care in 2006 but went instead to the experimental therapy of olmesartan and now does not need oxygen, is very active, just did a sea kyaking trip without any oxygen at all and walked a half-marathon without any oxygen at all.

So this is the sort of improvement we are seeing when the innate immune system is reactivated to help people recover.



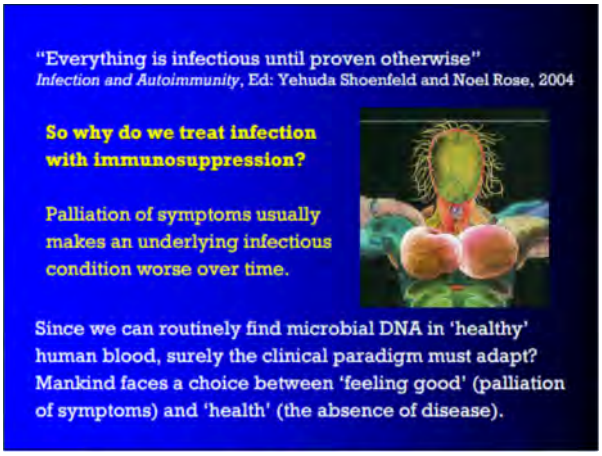
17:58

The problem, of course, is immunopathology. Because when the host resistance kicks in here, then there is always some damage caused by the immune response—the Immunopathology. That has to be managed.



18:11

Immunopathology changes with time. Unfortunately, the symptoms get worse before they get better. You can see here there is a peak in the ANA of this arthritis patient, and this ankylosing spondelitis patient also gets worse before they start to resolve.



18:28

Let us go back to the start again:

"Everything is infectious until proven otherwise."

The question is, why do we treat infection with immunospression? Palliation of symptoms usually makes the underlying condition worse over time.

We now can routinely find microbial DNA in "healthy" human blood using modern sequencing techniques. So, surely, we have to adapt the clinical paradigm. We have to understand we are dealing with microbes inside people and not just symptoms that have to be palliated.

Ultimately, this may come down to a choice for mankind, between the current paradigm of feeling good, palliation of symptoms, and a choice for health, the absence of disease long term.

19:18

I am going to talk more about TB in my next presentation which is on Saturday [October 20, 2012], mid-day, so those of you that can get to that presentation I just want you to know I will talk more about TB in that particular one. Particularly, drug resistance and how it relates to the microbiome.

Thank you.

Moderator:

One minute for quick questions.

Question:

What is the name of the drug you used?

Marshall:

We used a drug which was approved by the FDA in America for high blood pressure called a Sartan [spelled], a drug called olmesartan medoxomil. We found that olmesartan medoxomil was unique in that when we changed the dosing, it targeted other

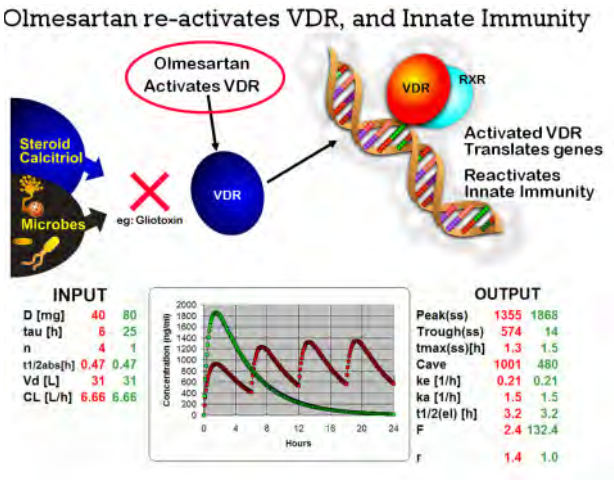
receptors beside the angiotensin-II receptor that it was designed to target. So it was olmesartan medoxomil is what we found was useful.

Question:
What are the doses and what is the duration of treatment?

Marshall:
The duration of treatment is very long. Hardly anybody responds within the first two years. They start to respond clinically, typically, at beyond the two-year point. The disease resolution typically takes three to six years. The patients often get better beyond that, particularly in terms of cognitive and memory issues.

So effecively, we are talking about a disease that takes a lifetime to gradually come on and which takes about a decade to fully get rid of.

It is not a quick fix at all.



The dosing is 40mg, every four to six hours, of olmesartan medoxomil. It is what we use. So that keeps the blood levels—if you remember the slide—you can see the blood levels stay below what is known to be safe for that drug.