00:00
[APPLAUSE]
00:02
Thank you for having me here--
00:03
more importantly for having ME/CFS
00:07
among the topics for the library.
00:10
I don't see any other disease that has humbled me the most,
00:16
has terrified me the most, and at the same time
00:20
has propelled me the most to try to find answers--
00:23
to seek answers.
00:27
What I would like to do tonight is present
00:29
an example of a case of a patient,
00:31
that we just saw literally this week.
00:35
And it's just one example of many
00:38
of the million and more Americans-- probably
00:41
way more than a million Americans--
00:43
a million people worldwide who are presenting with this.
00:47
This is just an illustration of how this terrible disease
00:52
continues to strike humans.
00:56
I'm trying to avoid some personal information,
00:59
but she gave me permission to do this.
01:01
Young, healthy, active American woman
01:05
who developed full-blown chronic fatigue syndrome in 2013.
01:10
She was born in the Midwest--
01:12
no health problems growing up, always physically active,
01:17
and at the same time academically accomplished.
01:20
Outdoor lifestyle, long, intense hiking trips--
01:24

she will take that Pacific Trail from Northern Mexico all
01:27
the way to South Canada, and do that in one trip--
01:34
average hiking distance 50 miles a day.
01:37
Full time job as an environmental engineer.
01:40
Happily married to the most beautiful guy
01:42
you can see as a husband, am example for many of us.
01:47
Denies a history of depression or
01:49
of any other psychological problems.
01:52
This is one of the most striking things with this illness.
01:55
And those who still don't believe in the illness
01:58
don't see this, how healthy and active people were
02:01
before the illness.
02:04
And one of the main findings that led me as a physician
02:08
to see that there was no possibility
02:10
that these patients were faking an illness when
02:12
they had this life.
02:16
In 2013, during one of her trips,
02:19
she developed classic herpes zoster.
02:23
This is the same virus as chicken pox
02:26
that people usually get in childhood,
02:30
and is the same virus that later in life
02:33
can get manifested with what we call zoster.
02:36
Zoster is very classic, because you
02:38
have those areas that we call the vesicular,
02:42
and they tend to have these what we call radicular distribution.
02:47
In this case it was a V1 ophthalmic branch.

02:52
An ophthalmologist has to see these patients to make sure
02:55
that the eye is not involved.
02:56
And it can lead to serious problems in the eye.
02:59
And she had it right there in where
03:01
you see in the forehead on the left side and also the scalp.
03:07
We don't have pictures of the scalp,
03:08
but this is classic zoster.
03:10
It was so classic that she received acyclovir
03:14
with resolution of the pain, and one of the feared complications
03:18
of this infection is that the patients may go on for decades
03:22
with their horrible pain.
03:25
And she did not have that-- lucky.
03:27
However-- why is it that some will
03:32
have this infection, will resolve it,
03:36
and they will go back to normal, and others
03:39
will have, like in this case, followed by chronic fatigue
03:44
syndrome?
03:45
Something went, according to her,
03:47
wrong that she had never faced in her life--
03:51
extreme fatigue, limitation for her normal physical activities
03:55
weeks after the herpes zoster event.
03:58
Unable to walk for a few blocks without feeling
04:01
extremely exhausted.
04:03
She had to lie down in bed.
04:05
Even normal events like showering,
04:08

walking to groceries, became taxing
04:12
and were exhausting for her.
04:14
Even grooming her hair.
04:16
She was trying to push forward in her daily activities.
04:19
And who will not do this in desperation?
04:22
She felt that she will have more exhaustion
04:25
and she will be crushing even further.
04:27
She also noticed significant cognitive decline for someone
04:31
who was so academically accomplished,
04:33
with less ability to perform readings, writing emails,
04:38
significant [INAUDIBLE] finding difficulties,
04:40
and associated memory loss.
04:45
And I think that- in ME/CFS- the other thing
04:47
is that it's a disease for compassion,
04:51
but also for great clinical abilities.
04:54
You really-- and listening to the patient.
04:56
There is no way that you can, as you are seeing this unfolding,
04:59
that you're going to say that this
05:01
is the usual thing of somebody getting tired.
05:04
2013-14, energy level continued to decline.
05:09
And this is a nightmare that many patients go through.
05:11
They visit providers and they're told
05:14
that they have depression-- that they need to see a counselor,
05:20
that it's something that is psychological.
05:24
Very low levels of energy-- she had to quit job.
05:27
Unable to engage in other physical activities--

05:30
basic life, and also the cognitive
05:34
was taking her more downhill.
05:37
In 2015, this is not infrequent, patients
05:40
go a major clinic and many other places for an answer.
05:44
And she did not have anything in terms of tick-borne diseases.
05:48
It was attempting to say that she
05:49
could have a tick-borne disease because of her hiking
05:52
exposures.
05:54
However, she did find other physicians who
05:57
gave her multiple courses of IV an oral antibiotics which
06:03
make her sicker, because she had side effects
06:06
on the antibiotics-- diarrhea, more fatigue,
06:09
and left her worse.
06:11
She feels that the antibiotics did that--
06:13
no significant improvement.
06:16
2017 and 18, she establishes care
06:19
with a provider who thought that maybe there
06:22
was something on that herpes zoster episode
06:25
and it starts ongoing suppressive valacyclovir along
06:30
with other meds like trazadone, multi-vitamins, and gabapentin.
06:34
And since then, since September of 2017, for the first time
06:39
she sees that, consistently, she is
06:42
starting to get slight increase in her physical function
06:48
and cognitive.
06:49
She's now able to write e-mails and read.
06:52

And we just saw her now, so I don't
06:54
have an update of what happened after we see her,
06:57
but she decided to come for clinical care and participation
07:00
in our research studies.
07:02
And that has been initiated.
07:04
But this is not an unusual study of someone
07:05
who has an entire normal life and there
07:09
is a major event that can be, in this case, infection.
07:13
But we know of patients who have had trauma, surgery,
07:18
head trauma, pregnancy.
07:21
And if one tries to--
07:23
what is behind?
07:25
What is the commonality?
07:27
What is the common denominator there?
07:29
It's hard to ignore that it could be an immune response,
07:32
because when you have surgery, when you have trauma,
07:35
you trigger immune responses and the same thing with, obviously,
07:38
infection--
07:40
pregnancy, major immune systems, also shift
07:45
It's a serious issue.
07:50
It's a test for human mankind compassion and kindness,
07:56
because these patients go into such a desperate state
08:00
that some of them take their lives.
08:02
And this is a study in a relatively small sample
08:05
size from Lenny Jason, who is an outstanding ME/CFS researcher.
08:11
And he points out that there might be also

08:15
issues of these patients with ME/CFS dying earlier.
08:20
So if they're in the general population, most patients,
08:24
more individuals die around 73.5 years of age.
08:30
ME/CFS patients appear to that earlier,
08:33
have cardiovascular related events
08:35
earlier, suicide earlier, cancer-related earlier,
08:40
He acknowledges that this needs to be validated with a larger
08:44
sample size, which was done in the UK with this Lancet study,
08:50
where they did a group of CFS patients
08:54
in a larger sample size.
08:55
Unfortunately, they did have 2,147 cases,
08:59
but the period of observation was too short--
09:02
seven years.
09:04
Despite that they period of observation was shorter,
09:07
they did find increased suicide-specific mortality
09:11
in these patients.
09:12
And I cannot think how they will not at least think about that.
09:18
And we have lost, sadly, some of our patients
09:23
where hope could not reach them.
09:26
So this is a serious issue and has potentially lethal
09:32
consequences.
09:33
I think that one of the biggest mistakes made
09:37
by modern medicine is to have arrived to the conclusion
09:42
that diseases like ME/CFS, fibromyalgia, Gulf War
09:46
illness, chronic Lyme disease are a creation of the patients
09:51

imagination.
09:53
But these historical mistakes made
09:57
by many official government agencies and mainstream
10:03
medical associations has started to be
10:05
mended by what has finally taken place in the way of February
10:11
10, 2015, when the Institute of Medicine
10:16
came out with the report where, clearly, after reviewing 9,000
10:21
of articles or plus it was concluded that this illness was
10:26
real and needed to be researched.
10:30
And after Ron Davis, present here in the audience,
10:33
was one of the members of this group.
10:36
So this is one of the most respectable
10:40
scientific organisms concluding that there was no question
10:44
that there was scientific validity
10:47
and biological validity behind this illness.
10:50
And that has led to other organisms like NIH, and FDA,
10:55
and CDC to really rally behind this idea
10:59
of getting this solved.
11:02
For practitioners, I think this has made a big difference,
11:06
or can make a big difference, because one
11:10
of the challenges with this illness as a practicing
11:13
physician is that you are given very limited amount of time
11:17
to really see the patient.
11:20
And they have a history of five to 10 years,
11:22
and you have to do that in less than an hour.
11:26
And what this IOM work did very nicely

11:30
is to simplify the way that you can arrive at the diagnosis,
11:33
by basically asking five questions.
11:38
The first one is the fatigue.
11:40
And if the fatigue is not alleviated by rest,
11:42
if the fatigue really substantially decreases
11:46
that person's capacity to do work,
11:48
education, social by 50% or more--
11:52
so a significant impact in their lives
11:54
that doesn't go away by rest--
11:56
for more than six months, that's one criteria.
12:00
The second, unrefreshing sleep.
12:02
It's fascinating when you hear when you're
12:06
listening to these patients, they
12:08
will tell you that they do not wake up fresh
12:10
no matter what they did.
12:12
They have the issue that their sleep that we all
12:15
look at as that restorative process that we all,
12:18
as human beings should be entitled to,
12:21
it doesn't happen regardless of how long they sleep.
12:24
So that's a second cardinal feature of this illness.
12:28
And the third is that thing of when they push beyond--
12:32
and the threshold of what constitutes too much
12:36
for each patient is different--
12:38
they crash.
12:39
And it's what is described as post-exertional malaise.
12:42

And in internal medicine it's a whole fascinating world
12:46
of many diseases that have been nicely described
12:50
by centuries of good clinical observations, and research,
12:55
and laboratory work.
12:59
There is no other disease with these three features.
13:01
There is no other illness that have those three features.
13:07
So IOM in a fantastic way-- fascinating way--
13:12
arrived to this conclusion.
13:14
And when we apply this definition to every patient
13:17
we see new--
13:19
and we did a study and we went back to all the patients
13:21
that we have seen, and applied this definition
13:24
against the old definitions--
13:26
we find that it works.
13:28
So this is really a nice, important, practical tool.
13:30
that hopefully facilitates that patients
13:34
like the one that I showed you--
13:36
it took her five years to arrive to the diagnosis of CFS--
13:39
can be told you have CFS six months later,
13:42
or a year later, and not five years later.
13:44
And some patients have gone with this issue for decades of not
13:49
being diagnosed properly.
13:51
And the other two is you ask if they
13:53
have cognitive issues like that patient that I showed you,
13:56
or orthostatic intolerance issues.
13:58
And if they have the first three plus either

14:01
of the cognitive or orthostatic intolerance,
14:04
they have chronic fatigue syndrome.
14:06
So I think this is extremely helpful for practitioners
14:09
and for patients to be diagnosed earlier.
14:12
That this is a real illness has been editorialized
14:15
by Tony Komaroff, who has been one
14:17
of the most active researchers and witnesses of this illness
14:22
for 35 years plus.
14:25
And he titled this perfectly in this very prominent Internal
14:31
Medicine Journal, that this is a real illness.
14:35
And no question that if one wants
14:38
to throw the argument of economic impact, that for all
14:42
angles that you see from the productive years
14:46
that young patients lose, the many amounts of medical care
14:51
that goes into their expenditures,
14:54
that many people around them have
14:56
to take care of them that lose that ability also
14:58
to be in productive hours, the amount of money that is lost,
15:04
for an illness that by now should be understood
15:07
and should be having effective treatments is significant.
15:11
Four major NIH grants were awarded in 2017
15:14
for this illness.
15:15
That's a welcome addition to this.
15:19
One for Cornell, one at Columbia--
15:23
we are part of some of the Columbia work.
15:26

And at the Jackson Laboratory there
15:30
is a data center that will be coordinating all data
15:34
from the North Carolina site that
15:36
is famous for statistical work.
15:41
So I think that is helpful to have
15:43
at least that fresh air coming in the way of findings coming
15:47
from the NIH.
15:49
Probably the process for deciding
15:52
to whom the funding goes needs to be changed or fixed,
16:00
but we don't have time to go over how that went.
16:04
There are thousands of papers that
16:08
had been published showing objective abnormalities.
16:11
There is no question that if you do
16:13
exercise testing in these patients and tilt table
16:16
you will see abnormalities.
16:18
Natural killer cells continue to be a common theme.
16:22
It has become that every time that we have a new patient here
16:25
at Stanford, we do the natural killer cells, and at least 30%
16:30
of them have significantly low natural killer cells.
16:34
And that's an important argument of reflecting
16:38
why we do certain things in terms
16:40
of management and treatment.
16:42
Natural killer cells were placed by nature in humans
16:47
to defend against tumors and viruses.
16:52
And they have been really well conventional medicine studies
16:57
showing that if someone does not have natural killer cells,

17:00
they have really bad herpesviruses infections.
17:03
The whole literature on that area is well documented.
17:08
And CFS patients happen to frequently have
17:11
low natural killer cells.
17:13
And we have some of our patients who have no natural killer cell
17:16
activity.
17:17
So there is something that's a clue.
17:20
And we use that observation to emphasize
17:24
the potential role of viruses triggering the illness--
17:28
like the patient that I showed you--
17:30
or viruses perpetuating the illnesses, especially
17:33
herpesviruses.
17:35
There is no question immunological abnormalities
17:39
that have been reported, metabolic microbiome,
17:43
brain imaging studies--
17:46
obstacles for why if all this research has been done,
17:50
and we have not arrived to a question,
17:53
include the fact that this is really a tough disease.
17:56
It's not a disease for an average physician,
18:00
for mediocre physicians.
18:04
This is a disease for really tough ones
18:08
who like to take a challenge, because patients will come
18:12
to you with years of illnesses, and also will
18:16
come to you with many complaints from different systems.
18:19
So if someone comes with shortness of breath
18:22

and they have more shortness of breath if they walk,
18:26
they get even more shortness of breath when they lay down.
18:30
And you see their big veins here.
18:33
And you hear an extra third heart sound.
18:37
And the legs are swollen.
18:39
It's so easy to say that patient has classic heart failure.
18:44
But this patient will not present with anything classic,
18:46
they will have that story, and some other patient
18:49
will have a different story.
18:51
So you really have to be able to zoom in and out as you
18:55
are listening to the details to be able to say there might be
18:58
a unifying process here underlying
19:01
these various, different presentations.
19:03
So that might be one obstacle.
19:05
And it's that patient who clearly have the zoster
19:10
and follow the chronic fatigue syndrome--
19:13
should I take that patient different than the one that
19:15
had mono or EVB as their answer, or should that
19:19
be different than the one that has CFS after a trauma?
19:23
So it's complex, but that should not deter us to do the studies.
19:32
But it could be one of the reasons
19:33
it has been hard to conquer.
19:37
The lack of standardization in research methods
19:39
is significant.
19:41
So when you see studies it's hard to find
19:44
that the research methods align to what you should be doing.

19:48
Sample size is big.
19:50
I'll show you an example.
19:52
We were fortunate with that study
19:54
that we do with cytokines, but, obviously,
19:58
partly of why we were successful has
19:59
to do with the people we associated with,
20:02
but also with the fact that we had a sample size of 200
20:06
patients and 400 healthy controls,
20:08
and allow us to see something that was not seen before.
20:13
That it became obvious by the data that we were seeing,
20:16
we didn't have to force it.
20:19
And then the technology, obviously.
20:23
There were, in the 1800s, people dropping dead in London
20:28
with what we know today is cholera.
20:30
But back then, it was not any idea
20:32
that that's what was happening.
20:34
And only when principles of epidemiology and a microscope
20:37
were used that it became obvious that was viral cholera.
20:41
So it is possible also that we have not
20:44
had that kind of technology for so many years--
20:48
for decades.
20:49
But now, it could get us closer to what this illness truly is.
20:56
And so, infection is likely to be one of the big ones.
21:01
10% of patients who develop acute EBV, Q fever, West
21:08
Nile virus, [INAUDIBLE],, zoster virus
21:12

are going to have CFS after that event.
21:16
And many patients will tell you, yes, I had that infection,
21:20
and that's when my CFS began.
21:23
We got involved in a very timid way.
21:27
We observed-- I will always remember my first patient
21:32
February 2004, who came with big lymph nodes
21:36
and a lot of herpesviruses.
21:40
I can only claim that I was attentive to what
21:43
they were telling me-- the patient was saying.
21:46
I was very familiar with antivirals,
21:48
because I used them a lot in cancer and transplant patients
21:51
in that patient population.
21:54
If a physician could have a malpractice lawsuit
21:59
if they don't use antivirals, because they will die of this.
22:02
So I was very familiar with that.
22:04
And I used that drug, and the patient, months later,
22:08
my fatigue is gone and all that stuff.
22:11
So I did listen to that And it started in a very timid way--
22:14
very low-key way-- in 2004.
22:18
Then we went full-blown, and did a randomized, double-blind,
22:21
placebo-controlled clinical trial
22:22
showing that there was a benefit, even though the sample
22:24
size was small.
22:26
And then we got an anonymous donor in 2009
22:29
that really expedited things for us, where
22:32
we had been able to put together infectious diseases, neurology,

22:36
neuroradiology, GI, cardiology, immunology, genetics,
22:41
bioengineering, and the human immune monitoring center.
22:45
So it's only possible because it was
22:49
catalyzed by this funding that came from this anonymous donor.
22:53
And the group has grown significantly.
22:57
And we have the immune center, we have the HLA and blood bank,
23:02
we have neuroradiology, neuropathology.
23:06
We have now just started the brain bank.
23:10
But I hope that the brain bank doesn't
23:13
work-- that that study, that we don't ever
23:16
need to get any brain from any CFS patient.
23:20
We are now approaching the microbiome and the nutrition
23:24
with Chris Gardner.
23:26
Cardiology, bioengineering and infectious diseases,
23:31
bioinformatics-- bioinformatics is huge
23:33
because you get this massive amount of data,
23:36
and you have to have someone who will help you
23:39
with the processing of that information.
23:42
The studies include longitudinal studies following
23:46
patients over the long-term, and includes cross-sectional study.
23:50
And for that, we take advantage of the sample size
23:54
as I mentioned.
23:54
So this cohort of 200 patients and 400 healthy controls,
23:58
they have undergone cytokines.
24:02
We have issues with the gene expression,
24:04

so we're going to redo the study of the gene expression.
24:07
We were very unhappy with the data.
24:09
There were serious issues in that data.
24:11
We are excited waiting for the CyTOF.
24:14
It's a specialized test of the immune system.
24:17
And we have finalized the curation of the data.
24:21
It's a lot of data.
24:22
It's like 600 million data points for the entire study.
24:28
And the HLA data just came up, and it's positive.
24:33
So I'll now mention briefly about that.
24:36
And we have some studies looking at the electrical activity
24:39
of the brain-- the anatomy--
24:41
and the cardiac endothelial function.
24:43
So all these things are moving forward,
24:46
and we are very excited about that.
24:48
One study that was positive since the last time I spoke
24:52
here is the MRI-DTI study.
24:57
So in a small exploratory study we
25:01
found that the right anterior arcuate fasiculus in patients
25:06
was increased in certain areas compared to controls.
25:11
And the same thing with the right inferior longitudinal
25:14
fasiculus.
25:15
These are bandos-- they are fibers
25:18
that connect one area of the brain with another.
25:21
We were so happy when we saw this,
25:25
and we kept going back to the data.

25:27
The journal that publish this, Radiology, is tough.
25:32
So we already were tough with ourselves,
25:35
they were even tougher with us.
25:37
But because we have been tough with ourselves,
25:41
we were able to publish it relatively soon.
25:43
And what is even more fascinating,
25:46
the areas at the cortex that these bandos, these fibers,
25:51
touch in the cortex of the brain, they are thicker.
25:55
So something on the fibers, something on the areas
25:57
that they touch--
25:59
and also, they white matter was reduced in CFS patients.
26:05
So this is the arcuate fasiculus,
26:08
and you can see it connecting here on the temporal lobe.
26:14
And it's found that it's much expanded here in CFS patients,
26:19
and when he goes all the way to the frontal lobe.
26:23
And the areas that it touches are thicker, here and here.
26:28
And this is the inferior longitudinal fasiculus .
26:33
Our hope is that this can become a biomarker.
26:39
You can see here the right arcuate fasiculus
26:43
and the longitudinal fasiculus in yellow.
26:46
We are right now in the midst of trying
26:49
to validate this finding.
26:51
And it has been so sad that everything time we
26:54
had gone to the NIH despite that we have that publication,
26:58
we have the data, we have everything right,
27:00

we had the right team, there's always
27:02
been an excuse about the funding for the study.
27:05
But we decided to leave that behind.
27:09
And we have been seeking the funding.
27:11
And it looks like we will be able, hopefully,
27:14
within a year and a half, to see if we can tell the world,
27:17
we have something in the brain of these patients
27:20
that objectively shows that there
27:22
is this abnormality in the right arcuate fasiculus.
27:26
The fascinating thing is that he has
27:28
to do with areas of processing for language and word
27:32
finding, which is exactly what the patient will complain.
27:36
So we are very hopeful about this biomarker.
27:39
And the thing you can trust is that we
27:42
will continue to apply the most rigor,
27:46
that if we find something it will be real.
27:50
And we are not afraid to say, we didn't find it,
27:52
or that we find the wrong things.
27:54
So stay tuned for this potential biomarker.
27:57
These are the areas of the brain that the cortex are
28:00
thicker, where these fibers are touching the area.
28:04
And these are two separate techniques,
28:06
and they find something that is abnormal in the same place.
28:10
So it's even more hopeful.
28:14
This is what is called they receiving operating
28:16
characteristic curve, where you want

28:19
to have very low false positives,
28:22
and you're going to have a lot of true positives.
28:25
And for this test, if we show that it's
28:28
the biomarker has been waited for in the brain,
28:33
it performs extremely well for a clinical test.
28:37
So we're waiting to see what happens.
28:41
This is the study that we did with cytokines.
28:45
And the idea was to see if we measure many cytokines
28:51
at the same times-- cytokines, as you know,
28:53
are these small molecules that the immune system uses
28:56
to communicate one cell with the other.
29:00
And you can find them easily in blood.
29:03
The one thing that we did on purpose
29:05
is that we needed to get a large sample size,
29:08
so we got close to 200 cases and close to 400 healthy controls,
29:14
and we paired by them by age so that age
29:16
was absolutely the same.
29:18
And the sex distribution, it was the same.
29:22
77% here, 77% here.
29:25
We have a little bit of an imbalance in the ethnicity,
29:29
where we end up having more Caucasians in the CFS group
29:34
than in the control group, but, statistically,
29:37
you can't control for that, to make sure that that will not
29:39
explain the differences.
29:41
And you can see here that most of our patients for sure
29:45

have the ION criteria, since many of them
29:50
will have close to 96% impaired memory,
29:54
unrefreshing sleep, 97%, post-exertional malaise, 97%.
29:59
So they were truly CFS patients without any question.
30:03
And the first thing is that we were disappointed
30:07
because we found very little differences between the two
30:10
groups.
30:12
You know, you invest all this effort, and money,
30:16
and resources, and you only find that one cytokine transforming
30:20
growth factor beta was elevated without any question.
30:25
So when we give you findings, they are without any question.
30:27
We spend a lot of time making sure that they are real.
30:31
And then their resistance was lower.
30:34
Now, they transforming growth factor can be very important.
30:38
So that cytokine has been found elevated in CFS patients
30:42
in at least five previous studies.
30:46
And it's a cytokine that, for example, tries
30:49
to decrease inflammation, but when too much inflammation
30:52
is going, it does the opposite.
30:54
It increases inflammation.
30:56
In animal models in early phases of inflammatory responses,
31:01
DFBETA along with IL-10 placates inflammation,
31:05
but when the process goes too far it becomes detrimental.
31:10
DFBETA also, unfortunately, has been
31:12
found to promote lymphoma development and worsening
31:16
lymphoma.

31:17
And patients with CFS have a heightened risk of lymphoma.
31:20
So we are wondering if this is the biological link
31:25
between the propensity that patients with CFS
31:28
have to lymphoma with that malignancy.
31:34
And then, DFBETA is also frequently found
31:38
in Ehlers-Danlos.
31:39
And patients with Ehlers-Danlos or hypermobility, they
31:42
have lots of patients with CFS.
31:44
So it may be also there.
31:47
We are not certain whether this should
31:49
be the therapeutic target, but we
31:52
are thinking in clever ways that maybe
31:54
have five to 10 patients, inhibitor DFBETA,
31:57
and see the clinical response.
31:58
But it could be a therapeutic target in these patients.
32:02
What we were really astonished by--
32:04
and I will never forget that morning in March
32:10
in California when we saw this data.
32:13
We did have it as a check-box.
32:15
We said, we have to check whether duration is important,
32:19
whether severity is important.
32:22
This data literally spoke to us.
32:25
We were not expecting it.
32:27
We knew we had to do the analysis,
32:29
but we did not know that it was going to come so clear.
32:33

So if you see in the x-axis you have four groups of patients.
32:37
The first is the control.
32:39
Then you have patients with CFS with mild, moderate,
32:44
and severe disease.
32:45
And in the y-axis you have the level of the cytokine.
32:49
And what was striking was that seven of those cytokines
32:52
follow in an upward trend the severity of the illness.
32:58
The milds tend to have on the low side--
33:02
the milds will be in the middle, and the severes
33:05
will have the high.
33:06
That was that upward trend that was so striking to us.
33:12
Some of them were statistically significant different
33:15
than the controls in those two groups,
33:18
like IL-13 severe group, leptin in the other direction
33:23
for the mild group.
33:26
And when you have this, you have to be careful
33:29
that you don't get too excited, and that you don't apply
33:33
things that are not there.
33:34
So we were heavily paralyzed by our statisticians.
33:39
And we asked them a simple question,
33:41
which of these upward trends are significant?
33:45
And statistically significant, that
33:47
doesn't mean that it's biological
33:48
is [INAUDIBLE] relevant, but it's
33:50
a little bit-- it gets you closer to biological truth.
33:54
And after heavy penalization, they found 17 cytokines.

33:58
We found 17 cytokines in which the upward trend
34:03
was clearly significant.
34:06
And, obviously, the next stop is to sit down in the dark
34:12
alone and think about what this could mean.
34:16
And it became obvious that 13 of those 17 cytokines
34:22
were pro-inflammatory.
34:24
They were promoting inflammation.
34:26
They were making more of the things that
34:32
give pain to patients, and makes them feel sick.
34:37
Many patients will come to you and say,
34:39
I feel my brain inflamed.
34:40
I see that my whole body is inflamed.
34:43
And things like, for example, interferon gamma--
34:47
that is used to fight viral infections--
34:50
IL-17, leptin, get a [INAUDIBLE] factor [INAUDIBLE] macrophage
35:00
[INAUDIBLE] factor--
35:01
all these cytokines are worsening inflammation.
35:05
And the more severe that disease, the higher those
35:09
cytokines are.
35:12
And that association, in science,
35:17
you cannot necessarily say these cytokines are causing chronic
35:21
fatigue syndrome, because chronic fatigue syndrome might
35:24
simply be the disease that is causing the increase
35:29
in cytokine.
35:30
But it's very striking the association with the severity.
35:38

And that has led us to propose that it might be responsible--
35:43
if we are correct-- that chronic fatigue syndrome
35:46
is a cytokine storm that goes chronic.
35:52
There is good evidence of acute cytokine storms doing real harm
35:58
to patients.
36:00
The most recent thing that is novel--
36:04
that is all in the new literature in medicine--
36:07
is with the use of these checkpoint inhibitors
36:10
for cancer, or CAR T-cells, where
36:13
you take the T cells of a patient
36:16
and you engineer the T cell off the patient
36:19
to attack it's own B-cells, specifically
36:22
the CD9 receptor in the B-cells which have cancer.
36:27
And those T-cells from these patients
36:29
are taught to kill the B-cells from [INAUDIBLE] patients
36:31
are given back to the patients, and they attacked that tumors.
36:34
And there are beautiful responses
36:37
in lymphoma and leukemia, especially lymphoblastic
36:40
leukemia, with these CAR T-cells.
36:42
Those patients have these horrible
36:45
what is called cytokine storms, where these cytokines
36:48
that I showed you cause fever, and confusion,
36:52
and fever hypotension, hypoxia, long respiratory problems,
36:59
inflammation of the brain.
37:01
So what we are proposing here is a model
37:04
of a disease where those very same cytokines that acutely

37:08
can cause horrible things to patients
37:11
may be doing this in an ongoing, chronic, unabated fashion
37:18
to CFS patients.
37:20
If you take those 17 cytokines and you start the group
37:24
them by what they could do, it's very tempting to see,
37:28
for example, CCL11, IL-4.
37:32
IL-5, IL-13.
37:34
And when you go and check, what are the main things that they
37:37
do humans?
37:40
Very similar-- eosinophil trafficking, IGE,
37:45
eosinophil growth, differentiation.
37:48
So that commonality in those cytokines
37:52
is all these hypersensitivity that the patients have
37:56
to drugs, to toxins, to environmental stimulants.
38:00
It's really tough for patients, because, for many of them,
38:05
anything will send them into a crash.
38:08
Anything-- even breathing, or anything.
38:11
And it could be that is based on this group of cytokines that
38:17
produce that biological effect.
38:21
The other way to group them is by the induction
38:24
of inflammatory states that had to do with the innate immunity
38:29
or adaptive immunity.
38:31
Or some of them will do innate and adaptive.
38:34
Unadaptive, adaptive.
38:36
Innate unadaptive.
38:37

And when you close your eyes and you see this data,
38:41
you say, no wonder why this patient has
38:43
been so sick for so long, and no wonder
38:46
why we have not been able to come up
38:48
with an answer for them.
38:50
But also, it warns us about doing
38:54
interventions for the immune system that are narrow.
38:58
I know that we are all disappointed
39:00
with the rituximab data that just is about to come up
39:04
in the form of publication.
39:05
But I think that there is now enough people talking
39:09
about it that I feel comfortable to say that it was negative.
39:12
And we were very hopeful for that trial in Norway.
39:16
And I think this explains it, because the rituximab is just
39:21
a CD20 B-cell blocker.
39:24
And B-cell is just one component of the adaptive immunity,
39:28
and has nothing to do with innate immunities.
39:31
So you are just tackling one component-- very
39:35
narrow component.
39:39
Another example of cytokine inhibition
39:41
for patients with chronic fatigue syndrome that is not
39:45
likely to work, and it showed that it did not work,
39:48
was this cytokine inhibition with Anti-L1.
39:52
This is a cytokine against an interlocking one.
39:58
And it didn't work.
40:00
It was [INAUDIBLE] only for four weeks,

40:01
so that was another mistake, or another problem.
40:04
For CFS you have to intervene years not weeks.
40:09
And it was not effective.
40:11
But it's not a surprise, it was just targeting one thing.
40:16
To illustrate the complexity, this is a study out of Columbia
40:19
that our group was part of, where
40:23
a combination of metagenomics and cytokines--
40:29
so gut microbiome and cytokines were put together.
40:34
And when you analyze three axises of data
40:38
that are complex on their own, and you
40:41
do what is called network analysis--
40:43
like a topological analysis of gut microbiome, cytokines,
40:48
and metabolomics in blood, you can separate patients
40:53
who have controls here.
40:55
You could have CFS patients without IBS and CFS
41:00
patients with IBS.
41:03
So the thing that is hinted in is,
41:06
sample sizes, complex technology,
41:09
interaction as a way to move forward--
41:11
this illness, hopefully to effective treatments.
41:16
I mentioned to you the work that we did with the cytokines.
41:20
And I'm happy to report that we have HLA findings.
41:23
We have HLAs that increase the likelihood of patients having
41:28
CFS, HLAs that increase the likelihood of patients having
41:33
severe CFS, and HLS that increase the likelihood
41:36

of having mild CFS.
41:37
So that thing about, why me, or why I end up in bed,
41:42
and that other patient is still functioning,
41:46
may be explained through genetics.
41:49
And one of the things that we have decided in our group
41:54
is to reach out to Ron and to Ron's group
41:57
for that publication, because we really need
42:00
to have the input on that area.
42:04
But we have, in that same patient population of the 200
42:08
patients 400 healthy controls, HLA predisposition
42:13
for the illness.
42:16
What we do in the clinic--
42:17
this research-- in each patient we get complete CBC,
42:23
comprehensive metabolic panel, thyroid function tests,
42:27
sed rate, and we do herpes--
42:30
we emphasize herpes-- and NK cell function.
42:33
Often, again, these patients have very low NK cell function.
42:37
And depending on the epidemiology,
42:39
we go into these tests.
42:43
There are some patients that will have ME/CFS,
42:45
and it will have something unique, and this is CFS leak.
42:51
So pay attention to that possibility.
42:52
They will tell you headaches are prominent
42:55
and headaches when they stand up.
42:57
And they have the orthostatic symptoms very prominent.
43:01
So we have a student from Germany

43:04
who came to see us years ago, the classic thing-- very thin,
43:09
very tall, long arms, some hypermobility,
43:13
but not that much.
43:14
We saw him with a CFS--
43:17
did extremely well with valganciclovir anti-viral
43:20
and an anti-inflammatory hydroxychloroquine, Plaquenil,
43:24
and went back to normal.
43:26
Then he comes back for a second bout of illness.
43:29
And this time we cannot improve him at all.
43:32
And one of the providers thought about this, a spinal fluid
43:36
leak.
43:37
He was seen by Dr. Ian Carroll here at Stanford--
43:40
detected the leak, patched it, and he went back to normal.
43:45
And so, the initial phase one day
43:49
will be seen as a fascinating [INAUDIBLE] to work it,
43:52
because of the challenges that it brings you.
43:54
And this is an example of when the leak gets fixed,
43:58
the patient basically goes back to normal anatomy,
44:01
and in this case, function.
44:04
What we do now--
44:05
when we studied early, we knew very little.
44:10
But now we have a more comprehensive approach.
44:12
We have a non-pharmacological component,
44:16
nutrition supplements, management
44:18
of the post-exertional malaise is key.
44:21

And then we have a pharmacological approach that
44:24
includes long-term-- and now long-term is five years
44:28
for us--
44:29
anti-virals, anti-inflammatory drugs, immunomodulatory agents,
44:34
and others.
44:36
Heavy attention to their diet--
44:38
we are studying a study that has never been done--
44:41
even as a study that has begged to be done--
44:45
about what foods make worse or better patients.
44:47
And patients will tell you that it's not always obvious.
44:52
The anti-viral treatment-- there was this study
44:55
that was published in the New England Journal of Medicine
44:58
at the end of the '80s that completely abrogated
45:03
the possibility of anti-virals.
45:05
It was a study with 27 patients, and they gave antivirals
45:09
for a total of 37 days.
45:12
And obviously, they found that there
45:14
was no difference in treatment.
45:16
And based on that study, the whole thing
45:19
was abandoned completely.
45:21
I told you how we started with this at Stanford,
45:25
and after that very first patient in February 2004
45:29
we decided to do a study on elevated titers for EBV
45:36
and HHV-6.
45:39
We were just fortunate.
45:42
I cannot claim that I predicted it.

45:44
I had done certain things in that way
45:47
of thinking, and predicting, and modeling,
45:49
and this one was a good accident.
45:53
And in a group of patients, we do have a group of patients
45:56
that no matter how long they had been sick,
45:59
20 years, 50 years, this is the extent of their illness
46:04
before the drug.
46:06
They go up, and significantly improve,
46:10
and they go back to normal.
46:13
It doesn't happen in everybody, but there
46:16
is a growing number of patients that come with that history.
46:19
Is duration of treatment important?
46:21
Yes.
46:21
So we thought that six months was long enough,
46:25
and now we know that needs at least five years of sustained
46:31
anti-viral for that issue of the low NK cells.
46:36
This lead us to do-- the holy grail of clinical trial
46:39
is a randomized, double-blind, placebo-controlled trial.
46:43
So where you distribute the patient into two groups,
46:47
and one will get the drug, the other one will get placebo--
46:50
a sugar pill.
46:51
They both look identical, so patients
46:53
don't know what they're taking.
46:55
And the providers don't know what they're taking.
46:58
And despite that it was a small number of patients,
47:01

we got a statistically significant,
47:04
in certain clinical markers.
47:05
For example fatigue severity score,
47:08
the lower the better the treatment group
47:11
is statistically [INAUDIBLE] from the placebo group.
47:15
Their cognitive function-- patients will tell us,
47:18
my cognitive ability is x or y on each visit,
47:22
and on the drug, double-blind fashion,
47:27
the patients on the drug clearly told us
47:29
that their cognitive function improved
47:32
statistically significant, when the placebo group did not.
47:35
We never forget the several patients who will say,
47:39
I don't care on what pill I am, I am getting better.
47:43
I'm just staying with you to help you.
47:47
And when we broke the code, they were on the drug.
47:50
So clearly, there is something on that drug
47:53
that really helps the patients.
47:56
And then, we show that though that drug also changes
48:00
cytokines-- so it's a immunomodulator--
48:03
and another, Dr. Cory Weiss here at Stanford,
48:06
has shown that also decreases microglial inflammation.
48:10
So it's possible that it's doing it through that.
48:13
And then, remember that I showed you that patient with zoster?
48:17
We have another sub-group.
48:20
They tend to be women in their 50s, that
48:25
tend to have the herpes too in this area.

48:30
And we see that often and often with these unbelievably
48:35
horrible CFS symptoms.
48:37
And for these patients when we suppress
48:39
the virus for five years, almost always they go back to normal.
48:43
And please know that they have been sick for 10, 20, and they
48:47
have tried numerous things, and they have not worked.
48:51
So possible candidates for anti-viral therapy--
48:55
patients with ME/CFS who are PCR positive for HHV-6,
49:00
who actually have oral herpes, genital herpes--
49:03
clinically active-- shingles--
49:06
remember that shingles can be without rash.
49:08
And that's the diagnosis of a really good internist, where
49:12
they have the classical pain, never the rash,
49:15
and then you can say that's herpes, and they have the CFS.
49:19
High titers for those viruses, or those
49:22
who have ongoing fluctuating viral syndrome.
49:25
So we pay attention to these subgroups
49:27
to make them candidates for anti-viral therapy.
49:30
And these are the options for drugs that we have.
49:33
We tend to stay away from an IV.
49:35
We mostly use PO.
49:38
And we are now using infusion of CMV-specific T-cells,
49:42
or vitally specifically infusion of T-cells.
49:46
We don't feel comfortable with that.
49:47
We are not there yet.
49:49

We hope to be there.
49:51
The one part that we are really excited
49:53
is about drugs for inflammation given that cytokine data.
49:58
And we are slowly gathering a group
50:03
of patients who remarkably get better with these drugs
50:06
or combination of them.
50:08
Based on their cytokine data, there
50:10
is no way that one drug will do it.
50:13
Or it will have to be a drug that does lots of them.
50:16
And there is one candidate out there that could do it.
50:20
And we're trying to get, hopefully,
50:22
a sponsor to use that drug that inhibits lots of those
50:27
cytokines that you saw there.
50:28
So we are excited about that.
50:30
Finally, the model that we're trying to create
50:33
is every infectious agent that you
50:36
see here has been documented to lead into CFS when
50:40
the infection is severe.
50:42
And you can see here the shingles virus.
50:45
There is this initial protective immune response
50:47
that lead patients to go back to normal lives,
50:51
but there is something here that is abnormal in the CFS
50:54
patients that lead to immunopathology,
50:57
and perpetration, and fluctuation of their symptoms.
51:01
And what we need to know--
51:02
what we are trying to do is, what

51:04
goes wrong from protective to pathology
51:07
is an unknown pathogen. It's a reactivation
51:10
of those herpes viruses, or a process
51:13
that has nothing to do with infection
51:15
but clearly self-perpetuates the process.
51:20
So I hope I was able to give you an overview of where
51:24
we are in our group.
51:28
Every time that you think about this disease,
51:30
it's very hard not to think about how much
51:35
we have failed these patients, the many patients who
51:38
have taken their lives, the many patients who
51:40
are still extremely sick.
51:43
And I think that we need to still move.
51:46
I always go in silence to this non-denominational church
51:51
here at Stanford.
51:52
I always read this part, "We must not desire
51:56
all to begin by perfection.
51:59
It matters little how we begin, provided that we are resolved
52:06
to go on well and end well."
52:09
And nothing of what I've done here today
52:12
would have been possible without the generosity of our donors.
52:16
Thank you.
52:17
[APPLAUSE]
52:27
Questions.
52:33
Yes.
52:34

Hi.
52:35
I wanted to thank you for your presentation and all
52:39
your hard work.
52:39
It's been amazing just following this.
52:42
I am an ME patient myself, and I also
52:46
appreciate the work of Dr. Davis, who has Generously
52:50
shared his time and his research.
52:52
And it's been a long journey in dealing with this.
52:59
And I have wondered--
53:03
you've been giving your information--
53:04
the generous information from Stanford--
53:07
the amazing website you have, guides that doctors can use.
53:13
You know, just across the street at [INAUDIBLE]
53:15
I had a doctor there, she's fantastic,
53:18
as many of the doctors are there.
53:21
However, when I brought this information to her, even
53:25
with my functional capacity tests and other tests
53:30
showing that I had ME, they told me, point blank,
53:35
after reviewing your information,
53:37
we do not prescribe vancyclovir.
53:43
They do not do antivirals for CFS.
53:46
And it's very difficult for patients in general
53:52
to bring this to their doctors.
53:53
It often, like you said, takes a very long time.
53:56
But also, we're looking at something
53:59
where your patients are bringing these--

54:03
Stanford's one of the most amazing places on earth.
54:05
And when you bring research from Stanford
54:07
and your doctor doesn't honor it,
54:12
yet says that these are your symptoms,
54:15
and this is what you have, I'm wondering--
54:18
and I think many patients that can't be here
54:20
are wondering-- what recourse or things
54:23
can they do in order to receive this treatment?
54:28
I got a referral to your clinic, and I love you guys.
54:32
You're wonderful.
54:33
But your waiting list is long, because you guys do great work,
54:37
and there's a lot of other people that need help.
54:39
So that's kind of my question.
54:41
Yeah.
54:41
Thank you for your question.
54:43
The question is about how, despite that there
54:48
is some work coming from Dr. Davis's group, from our group,
54:53
from other groups at Columbia, and other centers, when
54:58
you take the information to the providers and tell them,
55:02
look at this, it's real--
55:03
these guys at Stanford, or it could
55:06
be Columbia, it could be other places, are doing things.
55:08
And they're showing that there is something effective here.
55:11
And at least there is a group of patients with these drugs
55:14
that are getting better, try them on me.
55:17

You'll find this sad and blank response that, no,
55:24
I cannot do that for you.
55:27
And it's an impetus to do even more.
55:34
We are in full capacity, but we need
55:36
to do even more even at full capacity.
55:40
I know you want more things sooner, but with the CDC,
55:47
they have this weird association with Medscape--
55:50
I don't understand how they got together.
55:53
But we are going live nationwide to bring physicians
55:57
who see Medscape to try to send the message
56:01
that at least it's real, and there is this data somewhere
56:06
in one university academic center where some patients are
56:09
getting better.
56:10
So it's worthwhile to try the drugs.
56:13
Maybe what we have failed to do is to create simple protocols.
56:18
The valganciclovir is a drug, for example,
56:20
that is not easy to use, only because it
56:23
has all these warnings.
56:25
But those warnings are because all the literature
56:28
came from the transplant cancer patients and AIDS patients.
56:33
And in those patients they have so many other drugs
56:36
and abnormalities that the drug looks terrifying to physicians.
56:42
So I apologize.
56:44
I am so sorry that you received that.
56:48
But that's what we hear of other patients,
56:51
and it should not be that way.

56:53
I can tell you that once in a while you--
56:55
like that patient that I told you
56:57
that the physician decided to put her on valacyclovir,
57:00
not valganciclovir--
57:02
we are seeing that that's happening a little bit more.
57:05
Or I get email sometimes--
57:07
I had this vision on the antivirals for five years.
57:11
I stopped it and then they went down.
57:13
I put it back and they went up.
57:15
And then how long should I now have it--
57:20
telling me that others are following this.
57:24
I don't think we have the cure.
57:26
We are far from that, but we do have
57:30
a group of drugs that is really working
57:32
for a group of patients.
57:35
And hearing your story not only makes me sad,
57:37
but also that we need to do even more to bring this message out
57:42
there.
57:44
When I was in this conference call--
57:46
I don't remember, it was last night, or the night
57:48
before last night--
57:51
on this thing about the CDC and Medscape,
57:56
they told me that up-to-date-- this is a resource
57:59
the physicians use in the United States to get up-to-date
58:02
on what to do--
58:03

and fortunately it's still, for ME/CFS,
58:06
they we're recommending greater exercise
58:08
therapy and cognitive behavioral therapy.
58:13
So that's something that we're going to try to fight.
58:16
And it's going to be an uphill battle.
58:19
We got the CDC to remove that from the recommendations.
58:23
I'm very sorry.
58:24
I'm very sorry.
58:25
And we need to do more.
58:27
Yeah.
58:28
Yes.
58:29
Near the end of your talk you mentioned, I think,
58:32
that you were trying a drug that would
58:35
be broad spectrum in terms of dealing
58:37
with the cytokine storm.
58:39
But I don't think I listened carefully enough.
58:44
I wonder if you mind going over that a little bit.
58:46
Yes.
58:46
So with this data, you have to be open to the data speaking
58:54
to you.
58:55
And what I did is I went to several rheumatologists.
58:57
I would take my little thing, and say, if you--
59:01
and I didn't say it was ME/CFS--
59:03
have a disease with these cytokines
59:05
going up with the severity, what would
59:07
be the drug in your world of anti-inflammation efforts

59:13
that would best counteract these cytokines?
59:17
And they gave me always two responses, one prednisone--
59:21
steroids-- because that--
59:22
but, please, that's not the drug that we are thinking.
59:26
And the other one is Janus kinase inhibitor,
59:30
called tofacitinib.
59:33
Tofacitinib-- let's stay with the non-commercial name.
59:40
And so we really would love to do a clinical trial
59:44
with that drug, because it's the drug that base
59:47
appears to counteract.
59:48
And there are two generations of drugs
59:51
coming that do the same thing that we will also
59:56
explore as a possibility.
60:00
Yeah.
60:01
Could you spell that name?
60:03
T like Tom, O, F life friend, A-C-I-T-I-N-I-B--
60:11
Tofacinitib.
60:14
Thank you.
60:15
Sure.
60:16
Back in 1985 during the Lake Tahoe mystery illness,
60:20
a common denominator showed up right away.
60:23
All the clusters occurred in sick buildings.
60:25
Has anybody been interested in looking into that connection?
60:29
So the question is about the fact
60:31
that there were epidemics associated with buildings,
60:37

and has that been explored.
60:41
Not that I know of.
60:42
And we don't have the expertise or the resources to do that.
60:49
One of the things that we're trying to do
60:51
is not let our own expertise be a limitation in itself,
60:57
because you tend to sway things in the way that you know best.
61:02
And that's why we're trying to bring as many people that
61:05
are not in our specialty to enhance the possibility that we
61:09
find whatever this finally is without that limitation.
61:14
So we don't have that expertise unfortunately.
61:16
Sorry about that.
61:19
Yes.
61:19
How does one find a doctor who deals with that?
61:22
Oh, God.
61:24
So the question is how to find the physician who
61:28
deals with that.
61:29
So in this CDC thing that we are trying to create--
61:34
and there is another effort at the national level,
61:38
it's a committee that advises the Department of Health
61:42
and Human Services, that we advise them.
61:45
One of the things, there been this thing that,
61:48
do we bring all the information to everybody,
61:51
to all the physicians, or do you try
61:54
to create a group of physicians that is specialized
61:56
like the HIV doctors now.
62:00
And studies have been done in CFS patients

62:02
where the care is better if they know CFS than if they just
62:06
try to learn how on the go.
62:10
So what we do, is we go to this organization Solve ME/CFS,
62:14
and they have a list of the providers that do that.
62:20
Here in northern California, the Open Medicine Institute and us
62:24
are the two that do the CFS targeted care.
62:31
But we are way behind where we should be.
62:35
And if someone asks us if we are in New Mexico or any place
62:40
in the United States, we go to this organization
62:42
that seems to be the one that tracks better those physicians.
62:47
So that information is on the CGE, or?
62:51
It's Solve ME/CFS.
62:54
Is a website.
62:56
Solve ME/CFS.
62:57
So if I go on the website, I can find that?
63:00
Yes.
63:01
And the other thing is, if you don't mind, call our clinic
63:03
here, which is right here in the second floor,
63:06
and see if we can also help you with that information.
63:09
And we are-- the clinic here, the Stanford Hoover clinic.
63:14
Yes.
63:14
Yes.
63:15
And also, we are expanding the providers
63:18
so that we can, hopefully, see you and more patients.
63:21
We would like to see you.
63:22

Yeah.
63:25
Yes.
63:26
For those of us who've had the HLA markers done,
63:31
do you have the marker somewhere on the website or something
63:34
where we can view for those?
63:35
So we are finalizing the--
63:37
so the markers are there--
63:39
manuscript, and we want to have input from others.
63:43
I'm sure you understand that this is very sensitive.
63:47
We are now clear that that's what it is,
63:50
but before we publish it, we want to make sure
63:54
that everybody is in agreement.
63:56
And again, I would love Ron Davis's group and Ron Davis
63:59
himself to help us with seeing this data, making sure
64:03
that it's all squared.
64:05
It will come out, and then--
64:07
yeah.
64:08
Thank you.
64:09
Yes.
64:10
Have you identified and histopathological changes
64:13
in the brain tissues in patients with this?
64:15
[INAUDIBLE] the final, common pathway.
64:17
And if there's glial cell hyperactivation,
64:19
have you used low-dose naltrexone
64:21
for patients with just CFS and not fibromyalgia?
64:25
The question from Dr. Kenny, one of my favorite doctors

64:27
at Stanford, is about how we found histopathological changes
64:33
in the brain.
64:34
So there was a brain from a CFS patients from Temple University
64:39
where they did find, unfortunately, microglial.
64:43
And they found things that are on the side,
64:47
like a little bit of Alzheimer's, like plaques.
64:52
So there is precedent for the brain being examined,
64:56
and finding histopathological changes there in a CFS patient.
65:01
When the spinal cord has been examined,
65:03
they also find ganglionitis.
65:05
And the ganglia is the area where the herpes zoster
65:08
virus likes to go and cause inflammation.
65:13
The other indirect thing for your key question is, ,
65:17
there was a study in Japan where they injected a tracer that
65:23
goes to the microglia and they light up.
65:27
And I'm happy to share with you that the third active study--
65:31
so we have three studies, the DTI, trying
65:34
to validate that as a biomarker, we
65:36
have neuroendocrine study for women in childbearing ages,
65:40
and the third study is a neuroinflammation study
65:43
to see if we can see what the Japanese group saw
65:46
with a tracer that is more advanced.
65:48
It's a better tracer that goes to the microglia
65:52
to see if we see the microglial inflammation.
65:56
And not wait to have a brain to--
65:58

you know.
66:00
But we did create a brain biobank not expecting anyone
66:06
to research to commit suicide, but just if the patient dies
66:09
from another reason, then we are ready to analyze their brain
66:13
and look for those histopathological changes.
66:16
Thank you.
66:16
Thank you Dr. Kenny.
66:19
And would that be good news or bad news?
66:22
So the question is--
66:23
[LAUGHTER]
66:24
If you see histopathological changes,
66:27
will that be good news or bad news?
66:30
Every time that you see something, it can be reversed.
66:36
So if we see it, then the whole thing
66:40
will be just devoted to how can we reverse it.
66:43
So I know what you meant, bad news,
66:46
because that means that the brain is
66:49
affected, which we know it is.
66:51
So it would be good news.
66:53
Yes.
66:55
Dr. [INAUDIBLE].
66:56
Hi.
66:57
I just got this document about the common data elements
67:01
where they're trying to make lists of things
67:03
so that people doing research know what kind of patients
67:07
to put in their research, and what measures to use.

67:11
And I've also talked to people about that process.
67:15
And I've figured out that they're
67:16
refusing to put PEM in as something
67:20
required to have-- to say that you have to have that for CFS.
67:24
So I just wondered if you were involved in that,
67:27
and what you think about that, and if there's
67:28
any way you can help tell Beth Unger and the people
67:33
at NIH and CDC that that's kind of nuts.
67:36
Dr [INAUDIBLE] question-- it will not be
67:41
the first thing that is nuts.
67:42
But Dr. [INAUDIBLE] question is about,
67:44
there is this effort from the CDC
67:47
and the NIH called the Common Data Elements project.
67:51
The goal with that is to arrive to a common language
67:55
that all researchers will eventually use,
67:59
and the minimum information that you
68:01
need to have in your research so that the studies can
68:05
be compared.
68:05
And that's, in principle, a really good effort.
68:08
Dr. [INAUDIBLE] says that it appears
68:10
that there is some resistance to include PEM in this common data
68:15
that everybody should have, which
68:18
would be totally unacceptable.
68:20
I wasn't aware of that.
68:22
I got straight first-hand from people who have talked to them,
68:27

refusing to do that.
68:28
So I just wondered--
68:30
It would be--
68:30
If there was some way we could help, or you can help,
68:33
or we could together help, tell them that that's nuts?
68:36
Right.
68:37
Yeah.
68:37
No, I talk to Dr. Unger all the time.
68:39
We just were together at a meeting not that long ago.
68:42
So I'll find out what happened, because PEM
68:46
is one of the three diagnostic criteria from the IOM.
68:50
You know, it's hard for me to see if the patient the patient
68:54
has CFS if they don't have PEM--
68:56
that important It is.
68:58
And I think that PEM will be the single most important factor
69:03
in clinical trials being successful.
69:05
If you don't pay attention to PEM,
69:08
you could have a drug that is really
69:10
good appear like it didn't work, or a drug that is not
69:14
helpful doing the opposite.
69:16
More likely it would be a good drug
69:17
appearing that it doesn't work if you don't pay attention
69:20
to PEM.
69:21
So clearly you have given me an assignment tonight.
69:27
I'm glad I got it recorded, what you said.
69:30
[LAUGHTER]

69:31
I have a question on behalf of a friend who has
69:34
suffered from chronic fatigue.
69:36
And she'd like to know--
69:38
she's had chronic fatigue for 35 years
69:42
and has been recently given anitvirals--
69:45
what are the chances of this for benefiting?
69:48
And is there something else he can do besides drugs?
69:54
The question is that--
69:55
the person asking the question has
69:58
a friend who had chronic fatigue syndrome for 35 years,
70:02
she has recently been started on anitvirals,
70:05
what would be the chance that she
70:06
could get a significant response from there?
70:10
And what would be the other drugs?
70:11
One thing that we have found--
70:13
and we were not that good at the beginning--
70:16
is that it needs a comprehensive approach.
70:19
And one of the big known pharmacological ones
70:23
is this PEM issue.
70:25
It's really critical.
70:27
We just finished a study looking at PEM,
70:29
and I wish I could have had more time to show you.
70:32
But PEM is way more complex than we thought.
70:36
There are patients who get PEM an hour later,
70:39
and others will have it hours, the others will be 24 hours.
70:44

There are patients who get PEM a week later.
70:47
And so you could imagine--
70:49
and when you have, once again, in a few hours,
70:52
how do you study that?
70:54
And then if you study the PEM, the substances,
70:57
you have to pay attention to that.
71:00
We have not seen a single patient going back
71:03
to normal with the drugs that we have given them
71:06
that we have those stories if PEM hasn't been there--
71:10
it has not been conquered.
71:12
It has not been taken care of.
71:16
Family support is huge.
71:18
And this is really a test for compassion, us humans.
71:26
And then the diet can be big for some patients.
71:29
And there are patients who will tell you they went gluten-free
71:32
and clearly that helped them a lot.
71:35
And so the key thing for the antivirals
71:38
is that the benefit could be so imperceptible that patients
71:42
may think they are not helping them,
71:44
but it's only four or five years later
71:46
that you can see that there was a difference.
71:49
And these anti-inflammatory drugs
71:51
that can be different for different patients.
71:55
I'm sorry I cannot give you more specifics.
71:57
Thank you.
71:58
You're welcome.

72:00
Yes.
72:01
I was referred to your clinic early last year
72:06
and I was told that I was on the waiting list
72:10
and that I would be advanced to being
72:13
a patient by the end of 2017.
72:16
But I haven't heard from the clinic,
72:17
and I wonder if you have any idea what current waiting
72:20
time is.
72:20
Yes.
72:21
So this is a question about the waiting time in the clinic.
72:26
And I don't have the specific information about what
72:30
it is now, but I can tell you that we
72:35
have our second physician Dr. Hector Bonilla with us,
72:40
and we have a PA that, unfortunately, we lost,
72:44
but we're going to replace.
72:46
And Stanford is giving us support for more providers.
72:52
I feel really bad and sorry when I hear the stories that you
72:56
cannot get in, that you cannot get in.
73:01
We need more people to come and join forces with us.
73:05
Yes.
73:07
Yes.
73:07
Thank you.
73:08
You're welcome.
73:08
Sorry about that.
73:09
Dr. Montoya, it is 8:15.
73:11

Yep Thank you.
73:13
Thank you so much--
73:15
[APPLAUSE]
Englisch