DR. MILLER: Dr. Lund?

DR. LUND: With regard to the fact that we all show some signs of this disease in our joints, to what extent does genetic predisposition to this disease play a role? And is this a treatment for those with a genetic predisposition to the disease?

DR. ROVATI: I hope this is a question for the experts.

[Laughter.]

DR. LUND: Well, I'm just curious as to whether in your studies with regard to the longitudinal studies that have been performed, whether you got to the question of the genetics of the disease, basically.

DR. ROVATI: I was joking. It's an excellent point, of course, and, unfortunately, we didn't perform any genetics in any study, I must say.

DR. MILLER: Do you want to answer that question?

DR. FELSON: No, I don't.

[Laughter.]

DR. MILLER: Then you wait. You're not going to be helpful, you wait.

Dr. Harris?

DR. HARRIS: Yes, the question just posed I think is a very important one. In fact, it was one that I was going to pose, so I think we are basically on the same wavelength here. But not only do we have to worry about genetic predisposition, we also have to worry about states of development. And I just wondered, in your studies that you performed or the literature has now documented, is there any evidence of glucosamine may be more beneficial to the younger set as opposed to the older set? And do we have to make adjustments in that case to dosage or quantity that we need to achieve the effects we're looking for?

DR. ROVATI: The two studies, the two long-term studies, were pretty homogeneous with respect to the age of the subjects. They had on average 65 years, and the limits were actually between 55 and probably something more to 70.

Actually, one of the entry criteria was patients over 50 years as required for the guidelines for treatment of osteoarthritis.

DR. MILLER: Dr. Mehendale?

DR. MEHENDALE: Earlier, in response to a question, you included obese people as a possible population. A significant number of these are going to have diabetes or maybe already have in unawareness. And do you know the effect of this compound in such individuals?

DR. ROVATI: As I was mentioning before, there is currently no evidence in humans that glucosamine, any form of glucosamine, may precipitate diabetes in some way. Actually, we published a letter in the Lancet three or four years ago in which we were examining the blood levels of the patients in some of the earlier studies, short term, and in the long-term trial of Reginster.

While in the long-term trial of Reginster we had no patients with hyperglycemia at baseline and, therefore, I cannot answer to this question,

we saw, if anything, a decrease, a trend for a decrease in the glucose blood levels.

We examined the facts in some short-term studies. We had a reasonable amount of patients with hyperglycemia although they were not diagnosed as diabetic. And also in this case, we had no increase in fasting blood glucose.

DR. MEHENDALE: Do you have any information on insulin levels in these people who take this drug?

DR. ROVATI: We do not have from these trials. This was not scheduled. This is something that came out after the trials were designed. But I would like to mention one study that should be taken carefully for the reasons that I said before, because this is actually something done with a supplement of glucosamine hydrochloride and chondroitin sulfate, and they administered the substance for three months, if I'm correct, to patients with Type II diabetes, and they looked at insulin, they looked at glycated hemoglobin, and they found no change compared to placebo and no

progression in anything.

DR. MILLER: Dr. Felson?

DR. FELSON: [Inaudible, off microphone.]

DR. MILLER: Dr. Downer?

DR. DOWNER: You mentioned animal sources, particularly cartilage, as a dietary source for this. Would it be fair to say that vegans who are not physically active may be at greater risk for OA?

DR. ROVATI: I'm afraid I did not catch exactly--

DR. DOWNER: The vegans, the strict vegetarians, those who do not include animal products cartilage.

DR. ROVATI: I don't know if there is any epidemiological data on that. Perhaps Dr. Abramson and Dr. Felson...

[Inaudible comment off microphone.]

DR. DOWNER: You would be surprised. I have obese vegan patients. You would be very surprised. I think animal products have a role.

DR. MILLER: Dr. Krinsky?

DR. KRINSKY: This is not for Dr. Rovati, just for information. Two things.

One, in the Framingham Study that you've mentioned, are they, in fact, questioning whether the people are taking glucosamine and/or chondroitin sulfate?

DR. FELSON: Yes, but there's a lot of confounding by indication. You know, you can't tie--people take glucosamine because they have joint pain, and so there's likely to be an association of disease with glucosamine use. So you can't really test the preventive issue there.

There are ways now you could sort of get at that, propensity score stuff, but, you know, we haven't messed with that yet.

DR. KRINSKY: Okay. Thank you.

The other question is just informational. We have these written comments from Nutramax Laboratories, and I don't understand how they relate to our committee work. Were they solicited by the FDA or were they just free contributions?

MS. REED: They were just submitted.

DR. KRINSKY: Okay. Thank you.

DR. MILLER: I think at this point it's time for lunch. Thank you very much.

Lunch for the members of the committee and guest speakers is in the room next door, the break room. For everybody else, you're on your own.

We will return at 1:30 promptly to begin the session.

[Luncheon recess at 12:21 p.m.]

AFTERNOON SESSION

[1:30 p.m.]

DR. MILLER: This is the afternoon session. There are a couple of announcements that I have to make, and clarifications.

First of all, for the record, Mr. Michael McGuffin, who is a member of the Supplements Subcommittee and was supposed to join this committee for this discussion is unable to join us.

Second of all, I've been reminded that the phrase "prevention" is a term of art in drugs and "risk reduction" is a term of art in foods. And, therefore, we ought to be talking about risk reduction and not prevention. Since I've been doing that more than anybody else, I suppose I have to say mea culpa.

And, lastly, when you've finished talking using the microphones, please remember to turn them off. It confuses the AV person who gets too much extraneous noise.

This afternoon we begin with a presentation of Dr. Lee Simon of Harvard University

on the current state of etiology of osteoarthritis and modifiable risk factors. Dr. Simon?

DR. SIMON: Thank you. Good afternoon. I know everybody is bright-eyed and bushy-tailed back from lunch. I'm first up to be able to keep you awake for the next half-hour or so.

I am a rheumatologist by training, and for perspective's sake, I'd just like to make clear that I've been involved in this debate in that I was the former Division Director of the Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products in CDER, where I just left about five months ago. Furthermore, although my disclaimer is quite clear that I have no actual involvement in any company, pharmaceutical or nutraceutical or otherwise related to glucosamine or its congeners, I do have involvement in drug development consulting related to other companies in the field of rheumatology, particularly relating to disease-modifying agents as well as nonsteroidal anti-inflammatory drugs, which some of you actually know quite well.

I was charged by the organizers--and I want to give my thanks to them for asking me to come and giving me the opportunity to be in front of such an august audience, inclusive of colleagues of mine who are far more expert at osteoarthritis than I am, both at the biology or clinical study of such a disease. And I was charged with talking about etiology, pathogenesis, and treatment considerations, some of which you've heard a lot about already, but I'd like to highlight some of the important issues for the non-rheumatologic audience so that perspective can be gained regarding the discussion itself.

There is no question, as you've heard all along, that glucosamine actually has a benefit in the context of an analgesic effect of unclear cause. Whether or not glucosamine is a treatment that actually alters the natural history of the disease, i.e., osteoarthritis, remains entirely debatable and has a lot to do with trial design and outcome measurements. So osteoarthritis as a disease state is what I am actually going to be

talking about.

Typically, it affects people over the age of 50. The slide used to say "elderly," but as I've gotten older, I've obviously had to change that. A biologic process takes place which affects cartilage and, thus, as a result, there's a subsequent inflammatory component that characterizes most of the symptoms and signs of this particular process.

The clinical presentation is pain. Occasionally, patients will show up in my office and complain that, "I can't do what I used to be able to do." But having been a rheumatologist for 25 years, and although I had a boutique practice in an academic environment, I guarantee you I saw plenty of people who came in complaining of pain. And most patients don't come in and say, "I have an osteophyte." They tell me they're uncomfortable and something's wrong with their life.

And if you really look at epidemiologic evidence, it's pretty clear that are large number of patients who are over the age of 75--and I don't

see many of those people around this table, and we talked about this before. But over the age of 75, then a huge number of people, greater than 75 percent, will have X-ray evidence of this process. If you're over 85, 75 percent will be symptomatic. Now that we have more than a million centenarians alive in the United States, some of whom actually pay taxes, this is a very important issue to society. And it probably affects 16 to 20 million Americans, which is also an important issue.

You saw a similar slide to this before, but I'd like to point out that this is looking at the prevalence of all the rheumatic disorders that we consider. And, in fact, osteoarthritis, as you can see, is very frequent. The prevalence is quite high, and it's actually quite important. I'm not entirely sure that neck and back pain does not also reflect a manifestation of osteoarthritis in some circumstances.

So someone has already mentioned this, and I think it's really critical for us to think about this. Although the disease might be something

related to cartilage, the joint is a very complex organ. And the components, the mechanistic components of the joint, are all extremely interrelated. The mechanics of the joint is what we're talking about. So there's cartilage, and cartilage actually is a very interesting tissue. It's predominantly aneural. It's predominantly avascular. it's predominantly alymphatic. And it can represent within the joint two different sources of structure: hyaline cartilage, which is what we think of as the typical cartilage in the joint, consists of predominantly Type II collagen; whereas, fibro-cartilage, which is predominantly Type I collagen genetically, is what makes up other components of cartilage within the joint. Hyaline cartilage is really predominantly only found in the body in the joint--and just as an aside, in some other tissues, but predominantly in the joint.

What it's there for is to cushion and provide a particularly remarkable surface once changed to a degree by certain products such as hyaluronic acid and lubricin that can lead to

almost nearly a frictionless surface to allow motion to take place in very complex areas.

Then there are the menisci. The menisci are also cartilage, and they really consist of Type I collagen. There are other components to hyaline cartilage that we'll talk about in a minute.

Then there are tendons and ligaments, the joint capsulate itself. There's bone. There's actually the periosteum component of bone, and subchondral bone since the 1960s has been considered a very important component of transmission of forces in the normal, everyday use of the joint so that there's cushioning provided by an arcade of Type II collagen within the cartilage, but then the forces are also attenuated through the immediate subchondral bone.

Then there's synovial fluid, which provides nutrition in a certain way, but also some of the aspects that we talked about, about the frictionless surface provided by the components of synovial fluid, inclusive of hyaluronic acid and lubricin. And then the muscles surrounding the

joint, many people are common to say a good athlete, even they may have bad knees, by having excellent musculature can provide a lot of the support. And the evidence has been done over the years that, in fact, you really want to build up the muscles around a diseased joint to provide better support and better symptomatic control.

So here is what we talk about when we think about the idea of the joint as an organ. What I'm looking at here is just the bone, but here is the joint capsule and tendons. Here is the menisci. Here is the joint space. We've already seen and talked a lot about joint space so far. And in here is the hyaline cartilage lining the surface of the bone, which is the articular surface, the portion of the bone that moves through range of motion, predominantly. And you've seen a picture like this before, and these are the molecules of Type II collagen. And interposed between them are very important high-molecular-weight substances, the proteoglycans, that allow cartilage to be extraordinarily well-hydrated. So

there's a lot of water in this substance that leads to a lot of resiliency, a sense of being able to tolerate a lot of sheer stress and to not deform too greatly and be able to retain its format, so to speak.

There are multiple other forms of minor collagens which some people believe may play a very important role in progressive disease in some patients.

So there's been a lot of talk about risk factors for the generation of this disease this morning, most of which have already been actually discussed. Someone asked the question about genetics, and clearly, what we understand about genetics so far is that there are some people that have abnormal components of the joint, and those abnormal components might be, such as in Ehlers-Danlos syndrome, which is a disease of elasticity, a disease that, in fact, can lead to hypermobility because of increased range of motion, or more recently some people have discovered a Type II collagen defect in some families, and there are now

about 16 families in the entire world that actually have this Type II collagen defect, which then leads to a rapid and early form of osteoarthritis. So it's not a very common event compared to the numbers of patients who actually have osteoarthritis.

There's also been a recent identity of a new familial cohort with a form of increased chondrolysis. You get earlier dissolution of collagen and cartilage, and that also has been seen in two family cohorts.

So many of us don't believe that we have found the specific or singular genetic defect that might lead to osteoarthritis, and most of us believe that there is one. It may be eluding us, but there may be multiple different kinds of defects that, if they're genetic, might do that. Or perhaps there's yet an undiscoverable defect in some of the minor collagens that might be associated with the more common form of progressive osteoarthritis.

Then there are congenital anomalies that

are unrelated to these kinds of changes, such as a shallow cup where the acetabulum is in the hip that may lead to premature hip osteoarthritis.

Then there's trauma, and trauma obviously everybody understands that, and it can be quite unique and limited to the post-fracture scenario, the football player, or whatever. Then there are overuse syndromes, and Dr. Felson is an expert in identifying some of those people in Asia, for example, in China, who stoop all the time or who use chopsticks in a certain way that actually might lead to osteoarthritis of those particular joints. It's actually a fascinating phenomenon. The real question which I asked him last night on the plane was whether or not, in fact, if you then changed how they stood or changed how they used the chopsticks, introduced them to a fork, might that actually change the behavior and change, thus, the onset of osteoarthritis? I suspect that Dr. Felson would answer, but he certainly has the opportunity, to suggest that we don't know the answer to that question. And, therefore, some of the questions

that were brought up this morning as alteration of risk factors and that we'll talk about in a minute are clearly unknown.

Then there's a post-infectious state, such as patients who have rheumatoid arthritis or-- that's post-inflammatory, or patients who develop some form of streptococcal arthritis or other form of infectious disease of the joint that can lead to destruction of the cartilage and bone and, thus, without replacement might lead to secondary osteoarthritis.

Then many of us have discussed already and thrown out the terminology of obesity, and that clearly has been a risk factor and identified both from the Framingham Study as well as other epidemiologic studies. And now that we're in a Foods Advisory Committee, obviously it's a very important consideration and everybody knows that the epidemic of obesity has been on all of the front pages of all the major scientific journals, such as Newsweek and Time.

So, in fact, there is a clear issue that

obesity plays an important role in the inception and ongoing presence of osteoarthritis, particularly of the lower extremity. The other problem, of course, with obesity is: What does it mean to change it? How do you alter the disease state? Do we actually know that by decreasing weight significantly over a 30- to 40-year period you'll actually change the natural history of the progressive nature of osteoarthritis or change the symptoms, or will you change both? That's really yet to be defined.

There is yet another form of genetic disease that we don't understand which is a patterning of disease, and it's called hereditary osteoarthritis or hereditary osteoarthrosis, and I'll show you some pictures of that. And it's a particular clinical pattern of presentation of nodular osteoarthritis, particularly of the hands. Now, whether or not that is a major focus, I have no idea. I certainly look at my hands, and I remember my mother's hands quite well, and she had that significant event, and yet I have not yet done

that. And she developed it at the age of 50, and I am significantly beyond that. What genes are related to that still elude us.

So many of us try to think of osteoarthritis, knowing what we know--which is light years more than we knew ten years ago, but is still light years less than what we need to do to really understand this process--is we think of it as patients who have either normal cartilage and something happens, or patients who have abnormal cartilage at the inception of their being and something happens. So a very simplistic way to look at that is that the patient with normal cartilage and supporting structures is subjected to abnormally increased loads. And if you think about osteoarthritis as we think about it, it's predominantly in the lower extremity, and it predominantly affects those weight-bearing joints. And yet ankles are not particularly involved in osteoarthritis, and something else is happening in that regard; whereas, knees and hips are. And yet ankles also carry weight, and why that's exactly

sure, we don't know. So obesity and overuse syndromes may be examples of how that is affected.

Then there's the idea of the abnormal cartilage and supporting structures are subjected to either minimal or normal loads or abnormally large loads, and then you can think of inherited defects of structural components like I mentioned, defects of Type II collagen, a cartilage lysis syndrome, hypermobile syndromes. And then there are metabolic disorders that an lead to this where you get deposition of pigment that alters the characteristics of cartilage, such as in ochronosis. And some people believe that maybe even iron changes, as in hemochromatosis, may lead to some abnormalities of cartilage that could lead to these events.

However, the biology of osteoarthritis is actually now being elucidated much more clearly, and I grew up at a time when people actually used the term--and I can remember well training in an arthritis program at a major center, where I was told that osteoarthritis was "degenerative joint

disease," that this was not an inflammatory process, that it was entirely unrelated. And then Dr. Abramson taught me otherwise by convincing me that, in fact, there's an inflammatory process.

Regardless of that, it is a slowly progressive disease, and it's remarkably heterogeneous. Everybody in this room, as we've discussed, is probably at risk in certain ways or another. And if every one of us has this process, I guarantee you we would all progress in different ways based on our own uniqueness.

It's primarily affecting cartilage. There is an early cellular response. And as mentioned before by someone on the other side of the table, early on there's actually increased synthetic capacity at the cartilage, that there is actually an attempt to make more collagen, to make more proteoglycans, there's increased hydration because of that, and it's only subsequently later that, in fact, there seems to be a failure of the chondrocyte, the cell that's responsible for maintaining cartilage, that there's a failure of

the chondrocyte in its ability to actually make all of these things, and then you get progressive disease.

T8 Well, that's all well and good. It's all phenomenological. But whether there's actually any proof that those changes are truly related to the evolution of progressive disease is unknown.

And where inflammation begins to play a role in actually how this all evolves is very debatable. So you saw evidence by the Pelletiers and others that have been suggested that IL-1 and TNF alpha, two important cytokines that are primarily involved in rheumatoid arthritis, are involved here is true. But what their involvement and how important it is from a causality point of view is entirely unknown.

There is absolutely no question that synovial hypertrophy takes place in this disease. However, the extent of synovial hypertrophy is much less than you get in proliferative autoimmune disease such as rheumatoid arthritis. So with this hypertrophy, with this cellular change, we know

that inflammation is important. Exactly how important is unknown. And although it has been alluded to already that this may be a systemic process, it's not systemic in the nature of systemic like rheumatoid arthritis. It's systemic in the fact that whatever the abnormality to cartilage, whatever the abnormalities are that predispose this progressive nature, is inherently there. The systemic nature is not that there's a lot of inflammation so that you can measure a systemic response with CRP. So basically most of us would argue that this is actually a local event.

So, in fact, something happens at the cellular level which then leads to structural change, and you saw some pictures of that earlier. And then there's pain and other signs and symptoms that come along here. And I will reiterate this throughout my talk. There are plenty of people that have X-ray evidence of change and have no pain or symptoms. Do those people actually have osteoarthritis? Conversely, hardly anybody has osteoarthritis if they have symptoms and don't have

any change, as evidenced by an imaging technology that can help us make a diagnosis. But a diagnostic X-ray doesn't make the diagnosis. It is a supportive diagnosis of a clinical state as manifested how the patient presents. And that is ascertained by pain, functional limitations, and then obviously reduced health-related quality of life, which can then lead to actually the ultimate intervention, although I'm not a surgeon, of surgical intervention.

I love these dynamic slides.

So basically the pattern of joint involvement tells us something, but as a rheumatologist, because we have no--and it's already been ascertained, we have no specific blood test that tells us about a diagnosis, we have no specific ascertainment system, so we base it on clinical presentation. The asymmetry of joint involvement is very important and an overall way to look at somebody who shows up with pain and which joints are involved.

So to show you the dilemma--perhaps

rheumatology remains the last bastion of the diagnostician--basically you get certain joints that are involved and not other joints involved. So most people don't think that the MCPs, the metacarpal phalangeal joints, are typically involved in osteoarthritis, and that the DIPs, the distal interphalangeal joints, and the proximal interphalangeal joints are those that are more commonly associated when the hand is involved. Furthermore, the first cup or metacarpal is where at the base of the thumb, people think of this as a pretty traditional place, big toe, knee, hip, lower back, and neck, but not typically the thoracic spine. So it probably has something to do with the kind of plumb line that goes on with the body and where pressure relationships and weight-bearing or load-bearing takes place. Those of us who think about this a lot see a patient who presents with shoulder osteoarthritis, you think about a football player or some other form of trauma. Elbow osteoarthritis is considered incredibly rare without trauma, as well as wrist osteoarthritis.

So why is that? These are all diarthrodial joints. They all have synovial lining. Why are certain ones affected and not others? Furthermore, to contrast that, in rheumatoid arthritis the DIPs are almost never involved. So, unfortunately, the patterning of disease is important, and, unfortunately, without any other kind of biologic markers, were quite at risk. So the diagnosis of osteoarthritis is dependent upon several particular issues and, as mentioned, it's predominantly symptoms of pain, decreased function, or both, and you can see that with decreased function due to bony change, due to soft-tissue change or swelling, or due to alterations of the normal structures that can lead to change, some of which you can actually feel or sometimes even hear when a patient walks in with crepitance, and the crepitance is actually pieces of cartilage and bone within the joint space itself. We actually call those "joint mice," interestingly enough.

Then the other signs that can actually up

on physical examination include the asymmetry of the findings, the involvement of usually the large joints, something called Heberdens and Bouchard's nodes, which we'll talk about in a minute, which are the classic hand involvement of the distal and proximal interphalangeal joints with actually bony nodules, hypertrophy of the bony structure there associated most commonly with decreased joint space. Exactly what came first is still debatable. Bony swelling, some swelling and pain out of proportion sometimes to the inflammatory findings.

This picture, obtained from the American College of Rheumatology slide collection, is a classic example of bony involvement with Heberdens and Bouchard's nodes of the hand. Now, someone asked a question about the non-involved joint in this construct, and it has already been alluded to that likely the joints would be affected in some way, but they may not manifest themselves in this total manner. Not everybody has to have symmetrical disease with this form of presentation, and why the node is not in this middle finger

compares to this fourth finger is entirely unknown. And why one is more inflammatory than another without trauma, banging it, or whatever, is entirely unknown. So because of that, there's a lot that's unknown.

Furthermore, you can actually see this involvement here of the first cup or metacarpal with what we call squaring and an actual movement of the joint this way and can lead to significant alterations in function.

Then there's the imaging technology which is, in fact, becoming much more robust and mature with the development of magnetic resonance imaging. But basically, to date, the standard of imaging has been X-ray, looking either for the presence of osteophytosis, which theoretically and phenomenologically is thought to be biologic evidence of an attempt to repair, the idea that the mechanics of what's going on has led to hypertrophic change and new bone formation. Exactly whether that's true or not is entirely up to supposition.

Progressive joint space narrowing has always been mentioned throughout the entire morning, and it is a surrogate measure, we believe, of cartilage thinning. There may be other reasons for this to be taking place, such as mentioned with pseudo-widening. But, in general, most often it's associated with actual change in cartilage. And that's because cartilage is not well imaged by the X-ray. It is not dense enough to show up like bone is. And, therefore, it's not just space. There's not a lot of wasted space in the body. And it's not just open space. It's occupied by something.

But the problem, of course, is that this joint space narrowing is entirely difficult to predict. It is non-linear. It is believed that if you take an inception cohort of patients who actually have an evidence of osteophytosis and you actually study them over a several-year period--and there are several databases now to show this--only a small percentage, less than 10 percent, will within a two-year period show rapid change, such change enough to warrant a clinical study. By far,

the majority of the patients will have a slow progression and may not show enough change within two years to actually show a difference in a therapeutic intervention that might actually inhibit joint space narrowing.

So unless we can figure out some methodology to identify those patients who are going to have rapid change propensity, we're going to have a very difficult time studying that patient population for disease modification.

Then the idea of change in the subchondral bone has been unbelievably controversial because we don't know whether it's causal, so that if there are microfractures or there's edema, whatever that is, or if there is some other form of change such as localized osteoporosis due to the low-grade inflammation or disuse or change in weight-bearing or change in the function of the joint, that might lead to these microfractures and a change of transmission of forces, which then might lead to more forces being sustained on the cartilage, and might lead to new cartilage change. We don't know

if it's a causal event or it's a response to change in the cartilage. But when it's present, it clearly identifies a person who will have a moderate to mild inflammatory process that could be considered osteoarthritis.

So these are X-rays that show the example of what we've just talked about with increased bony sclerosis in the subchondral bone, joint space narrowing, as well as the development of osteophytosis, as well as some cysts that are considered important for association with osteoarthritis and malalignment.

So the imaging has been more sophisticated now with MRI, much more expensive; it's able to provide a 3D image of the joint as an organ, much better than the 2D image presented by X-rays. It also can help us understand this joint space that, prior to this, by X-ray is not clearly understood. And we can actually get an approximation of the volume of cartilage. So, therefore, in the future, I may be up here, if you ever invite me back, talking about this issue of cartilage volume rather

than joint space narrowing, a much more quantitative way of looking at this change. And it may be more indicative of the real effect of osteoarthritis. It may be able to identify early change in cartilage metabolism, and Dr. Felson and others were some of the first people to identify a change by MRI in the subchondral bone that initially was called bone edema, and now we know is not, and is probably related somehow a significant change in bone metabolism related to perhaps the inflammation going on in cartilage in that joint and perhaps related to the transmission of forces and perhaps something related to a change within the bone itself, perhaps due to microfractures or other change that's been induced by the change in cartilage.

We've also heard comments about biochemical markers. Well, I actually spent 15 years at the bench at Harvard studying biochemical markers, and I got out of it because I didn't see any future in it--not to suggest there may not be a future in it, but I certainly couldn't justify it

at that point in time.

In that context, there's plenty of sources for markers, because I've mentioned to you, although Type II collagen is predominantly in hyaline cartilage of the joint, there are other sources of Type II collagen; and, thus, epitopes that are related to synthesis or metabolism of Type II collagen may be sourced elsewhere besides the joint.

If, in addition, the joint is only affected in one place in the body, how do we know that what we're measuring that's systemic has anything related to that particular joint unless we're just measuring something in the joint fluid related to that joint? So it could be in the joint tissue or fluid, and you might find synthetic products of the components of the joint or products that reflect metabolism of the components of the joint. It could be found in blood circulating in serum, and it could be products of cartilage turnover, but which cartilage and from where and why?

It could be found in urine, and ideally that would be a nice way to do that. I did spend a lot of time doing that for bone, and there still isn't a blood or urine test for the diagnosis of osteoporosis.

The products of cartilage metabolism which are cleared by the liver or elsewhere, perhaps by the kidney, from the serum and then possibly further processed and then excreted in the urine. Obviously, this is a very promising way to go, but very frustrating. The biochemical markers are not yet adequate for diagnosis of osteoarthritis. It isn't yet adequate for identifying patients at risk or measuring outcomes, but they may be useful in exploratory studies, perhaps more so if we make them more robust. They may help identify at-risk or resistant patients, but not yet. They may help compare therapies, but not yet. They may help patients and doctors select and monitor therapies, but not yet. And it may help assess efficacy, it might be a surrogate endpoint, but not yet.

So what is an early marker versus what is

a surrogate? You've heard a lot of comments about this. Having been at the agency, I'm going to give you the definition of that, not because I continue to be responsible for what the agency says, but nobody had to check my slides, so I can be pretty clear about what the agency actually says.

A biomarker--biological marker--or imaging marker is a characteristic that is measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. It's important to remember that a clinical endpoint--I know you're going to know this, but, nonetheless, it's important to remember that it's a characteristic or variable that measures how a patient feels, functions, or survives. So, therefore, we're really talking about an intervention that might change someone's life, not just changing somebody's X-ray. It has to be symptomatically based. So a VAS scale for pain; a functional outcome in osteoarthritis such as a WOMAC or a HAQ; a patient global assessment. In

all ways, how has this therapy affected you in the last 24 hours?

A surrogate endpoint is a marker that is intended to substitute for such a clinical endpoint. So a surrogate endpoint, according to Bob Temple in 1995--and Bob Temple, for those that don't know, is the doyen of the FDA. Basically, a surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives; changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Well, unfortunately, we have no surrogate markers in the context of osteoarthritis, and, in fact, if someone was to ask me whether we actually have any surrogate markers in any rheumatic disease, I will tell you not. And I have had a lot of involvement in thinking about those in other diseases besides osteoarthritis. What we're left

with are clinical endpoints, and those clinical endpoints are the definition of a therapeutic response.

So I have actually been asked by the people at the FDA to answer specific questions that were posed to me as it relates to what you are considering based on what I've just presented. And I haven't even gone into the variability of an inception cohort versus a progressive cohort--the variability, as mentioned this morning that Dr. Felson said, about the differences in the risk factors associated with incident disease versus progressive disease. And that's because they are not yet totally understood or defined, and only people at Dr. Felson's level actually deal with them at this point in time. We don't know that Vitamin D actually truly plays an important role in progressive disease is osteoarthritis. And we really don't know what the role of obesity is from a causality point of view. But we do know associations.

So what valid modifiable risk factors or

surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? I gave you a list before of those risk factors as we understood them, and one example is obesity. This gives us a clear opportunity to enrich a study with more chance of having progressive disease by recruiting patients who are obese, and that has been shown by Ken Brandt's study of the metalloproteinase inhibitor, and that is shown by a recently publicized trial that failed of bisphosphonate in the treatment of progressive osteoarthritis as measured by X-ray outcome.

So, clearly, we can do something with the obese population and understand more about how to study a population by including obese patients. But, unfortunately, would I use it as a surrogate endpoint? No.

The other problem, of course, is what I mentioned, the low percentage of patients with progressive disease without evidence of actually incident or incipient disease.

So now what valid modifiable risk factors

or surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? Again, we know something about risk factors, patients with repetitive use syndromes, patients who are obese. What do we know about surrogate endpoints? Well, joint space narrowing is evidence of progressive osteoarthritis in most circumstances, but may or may not be associated with an important clinical component of symptomatology. We've already talked about that. Other observed X-ray changes are useful for diagnosis, but are not important by themselves without clinical symptoms of disease. So, unfortunately, really, it's not a surrogate marker.

There are no valid surrogate biochemical markers at this time, so the answer would have to be: What valid surrogate endpoints are there for predicting the risk of developing osteoarthritis in humans? None. What valid modifiable risk factors are there? Several risk factors. And they're modifiable, but that's for osteoarthritis as a disease that's symptomatically defined.

The other question asked was: Are joint degeneration and cartilage deterioration signs or symptoms of osteoarthritis? Well, yes. In the absence of another explanation such as ongoing systemic inflammatory disease or other things, there is evidence in the context of the symptoms of osteoarthritis that joint degeneration and cartilage deterioration is a sign.

Are joint degeneration and cartilage deterioration modifiable risk factors/surrogate endpoints for osteoarthritis? I would say not generally. The presence of the above finding are part and parcel to osteoarthritis. Joint space narrowing may be an important way to demonstrate that a structure-modifying drug may be active, but if there's to be improvement in the structure, it would be expected at some time that there might be a linked improvement in symptoms. If, in fact, that would happen, then joint space narrowing or progressive joint space narrowing might be a surrogate marker for that, but no one has ever seen that yet. And, in fact, as based on the draft

guidance document in osteoarthritis, generated by the FDA in the year 2000, it might be difficult to prove that. How long would you wait for a symptom change would take place in association with change in joint space narrowing?

So patients present with pain or other symptoms. Joint change and cartilage deterioration in some patients may be associated with pain and loss of function, but not all patients will have symptoms in the context of the observed change. Once a patient has pain, he will likely have evidence of change. But not all patients with change have symptoms, and that it's a spectrum of disease has already been suggested. But, in fact, is it a spectrum of natural degenerative process? Is it a spectrum of aging? Is Alzheimer's a spectrum of aging or is it a disease? Is lack of memory all Alzheimer's, or do people who get older sometimes become forgetful without Alzheimer's? And it's already been mentioned about LDL, HDL, hypertension, and other issues. Complicated.

So without--with, you know, talking about

osteoarthritis, you can't finish a talk without talking about therapy, and I was asked to also talk about therapy as it stands today. And basically as it stands today, it's designed to improve modifiable risk factors, so you reach ideal body weight in those that are obese. I have never actually achieved that in any of my patients. And as you can see, I have not achieved that in myself. Decreasing body weight probably does provide a decrease in symptoms. Do you alter lifestyle behavior such as associated with overuse syndromes? Jackhammer operators will tell you that they have to operate a jackhammer so they can bring food to their table. So it's not clear that you can always achieve that kind of behavior in an overuse syndrome. I'm not sure that Dr. Felson is going to be able to change the Chinese behavior of using chopsticks.

Now, in addition, we want to make patients feel better. We don't have anything that alters the natural history of the disease. So we use palliative therapy to decrease symptoms of pain,

leading hopefully to an improved health-related quality of life that's measurable either through some health assessment questionnaire or an SF-36 or other modality in a clinical trial. And by coming into the office to see your physician, answering the question, "How do you feel today?" with "I'm feeling much better." That's the inclusive use of analgesics and anti-inflammatory therapies, use of assistive devices to unload joints, use of cognitive behavioral therapy, and use of physical function and exercise therapy. There are yet no proven structure-modifying therapies, although there is some evidence recently that perhaps using a metalloproteinase inhibitor such as doxycycline in the right patient might make a difference, but that needs to be corroborated by larger studies and other studies.

I think I'm one of the few people in the United States or around the world that has actually participated in a double-blind, controlled trial of magnets, for example, that's recently been published. And, in fact, magnets don't work. And

you'll notice up here that I haven't said what I mean by analgesic or anti-inflammatory drugs.

I am co-Chair of the Steering Committee of a group called OMERACT, which is the Outcome Measures used for Rheumatic Disease Clinical Trials. OMERACT has been around for some time, and it defined what were the core outcome measures based on consensus that one would use in the study of osteoarthritis in randomized controlled trials. And basically what it showed--and by consensus of several hundred people interested in this field--that measuring pain, measuring physical function as opposed to disability, measuring a response to a patient global question, measuring imaging change over one year are the key important issues associated with ascertaining improvement in osteoarthritis, that biologic markers are way out here in the periphery, only because they're experimental as of yet, that the issue of stiffness is very controversial; that measuring characteristic markers of inflammation is hard to know what to do; that perhaps it will be important

to look at numbers of flares in an intermittent process; perhaps it's important to think about a fundamental and ultimate clinical outcome of altering the time to surgical replacement or other form of surgical procedure; and then perhaps also concomitant therapy where you use two or three therapies together and you measure the effect of an anti-inflammatory, an analgesic, based on how much rescue analgesic that they may use.

I have chosen to show you two different bits of data about where benefit lies and how much benefit a patient might see in a clinical trial using anti-inflammatory drugs. In 1991, Ken Brandt and others, in an article in the New England Journal, suggested that acetaminophen should be the first-line therapy, up to 4000 milligrams a day, to treat these patients for symptomatic osteoarthritis. Many of us have felt that with the evolution of an understanding that this is an inflammatory process, that that may not be enough. So this is actually a slide and a study looking at the use of two different COX-2 inhibitors head to

head versus placebo over a six-week period in patients who have flared osteoarthritis. And what I show here is not the fact that these drugs work. I actually show that the placebo works very well in this process for an acute benefit of pain over a several-week period. And, furthermore, the effect size of what a COX-2 inhibitor or a non-selective nonsteroidal may attain in this kind of expression is not overwhelming, that about 35 percent of the patients get 35 percent better with an anti-inflammatory/analgesic.

If you look at function--and this is measured by the Western Ontario and McMaster Analysis, which is, in fact, what most people use in determining outcome in osteoarthritis, you also see that there's a dramatic placebo response, but based on the size of the trials, there's statistical significance and change between what placebo brings to the table versus what is measurable by a nonsteroidal anti-inflammatory drug, in this context, selective COX-2 inhibitors.

However, Pincus and others--and I am

actually an author on this--have actually shown some very interesting evidence in a crossover trial which has its own problems, which we don't need to go into. But basically what they have shown is--and other people have suggested this as well, Fred Wolfe and others--that patient preference prefers the use of anti-inflammatory drugs rather than simple analgesics alone. This is actually two--

DR. MILLER: Dr. Simon, excuse me. Could you begin to summarize, please?

DR. SIMON: Yes, I'm almost done. There are two separate trials here, and basically they show in this context a nonsteroidal versus acetaminophen versus placebo, that there's actually much significant improvement with the nonsteroidal-like drug than the simple analgesic alone; and, most importantly, that patients clearly appreciated the effects of the anti-inflammatory drug over acetaminophen, whether you look at it in the context against placebo or against the acetaminophen directly.

So in that context, and in conclusion, I

think it's important for us to recognize that this is a heterogeneous disease with not a hell of a lot of understanding about the biology and where we're going. We have a process which is difficult to quantify, a process that's very difficult to study, a process where we have no structure-modifying therapies, that basically what we can really attain in a therapeutic approach is to make patients feel better. How to prevent this process without really understanding the basic biochemical, biologic changes that induce it remains elusive. And whether or not we will ever be able to answer that within my lifetime remains unclear.

So thank you very much for the time, and I appreciate being here.

[Applause.]

DR. SIMON: Thanks for the clap.

DR. MILLER: You have friends.

Any comments or questions? Dr. Krinsky?

DR. KRINSKY: I feel I'm beating a dead horse, but you have a slide that says, "A spectrum of disease, mild disease is still disease and

associated with changed joint tissue whether or not measurable by presently available techniques." Is that a cyclic argument that you're presenting to us? Because if you can't measure the disease, you're saying it's still a disease state. And could you clarify that for me?

DR. SIMON: Sure, but remember that I predicated the whole idea on that it has to be characterized by symptoms. So, therefore, anybody that presents with symptoms, whether they measure change by any modality, have the disease. If they fulfill the characteristic clinical presentation and in this context, if they have no X-ray or other changes, it might be a diagnosis of exclusion that you've ruled out other forms of arthritides. And for those that don't know, there are about 100 other forms of arthritis besides osteoarthritis. And the diagnostician has to then utilize the best characteristics of taking a history and performing a physical exam.

That's the nature of the circular argument because, without having biochemical or biologic

markers that are diagnostic of the disease, we're only dependent upon our clinical acumen. Ostler would be happy.

DR. MILLER: Dr. Harris?

DR. HARRIS: Yes, one very quick question--actually, two very quick questions. One is there's no evidence, I assume, that this disease is familial? And the other question I wanted to ask you was: Have there been any studies that have looked at an array of factors, such as DNA micro arrays or proteomics, in evaluating any changes?

DR. SIMON: Well, the second question is the easiest one to answer. In fact, that's what's going on now. Dr. Abramson already alluded to the fact that his laboratory has actually changed its focus into looking at those particular areas, about looking at array analysis. So that's one.

Two, there is clearly a familial behavior associated with this process. It's particularly evidenced by my allusion to hereditary osteoarthrosis, which are the Heberdens and Bouchard's nodes that are clearly seen in families

and you can actually do demographics associated with that.

I would suggest that many would argue that much of the disease is familially defined, and I suspect we just don't know the extent of how familial it may actually be.

DR. MILLER: Dr. Felson?

DR. FELSON: No critical comment afterward. I thought it was a lovely communication of complexity--

DR. SIMON: Thank God.

DR. FELSON: The remarkable complexity of this. And I think the committee also needs to get a sense that we're not so confused, that we don't have operational definitions of these things. We do. And I think that's perhaps one of the things we need to talk about briefly because so much of the questioning has been doesn't everybody have a little of this, how do you define this disease. And I think Dr. Simon repeatedly made a very important point, and the ACR definition of it, which Dr. Altman chaired the committee for, and a

variety of other epidemiologic definitions of it, including the definition that the Osteoarthritis Initiative at the NIH is using, require one--are fairly consistent. They require frequent pain in the joint, plus radiographic evidence of disease in that joint, almost always defined as a definite osteophyte. Okay? And that's the threshold above which we characterize somebody as having osteoarthritis. You'll notice that requires a combination of symptoms and radiographic findings.

The mild stuff is harder because there's a lot of people, and perhaps even some in this room, given the frequency of this disease, who maybe don't have pain every day or don't have pain on most days, but have it whenever they go up and down stairs, which they might not do every day, or when they play tennis or something like that. And they don't, therefore, meet the rigorous criteria we've just laid out if they don't play tennis every day or several times a week. Those people we might call having mild disease or, you know, something like that, given the fact that they're not plagued

by symptoms all the time.

But I think we do have definitions, I guess. You can see that they're an attempt to draw a dichotomous line, a line in the sand, on what we all recognize to be a fairly continuous process. That there--and both elements, both the symptoms and the structural abnormalities are continuous here. There's a little tiny osteophyte in probably all of your joints somewhere, okay? And yet the serious structural disease is present only in a few of you. There may be occasional symptoms--I can tell you I have occasional knee symptoms--in many of you, but not to the point where we would say it's beyond that line we've drawn in the sand, that is, on most days of the past month, for example.

DR. SIMON: But, David, we draw that line in the sand to allow us to homogenize our patient populations for clinical studies. You would have to admit that we don't as often draw the line in the sand when we make a clinical ascertainment whether someone actually has a diagnosis of disease. And that's the dilemma that we have

because often our clinical trials, particularly epidemiologic, are not necessarily extrapolatable to the mild case without X-ray evidence, but they have to be studied somehow, and you want to enrich your inception cohort with the possibility of change so that you can see it within the window of opportunity of a clinical trial. That's the challenge to know whether clinical trials are truly naturalistic and, thus, really inform you about this incredibly heterogeneous process.

DR. MILLER: Thank you.

Our next speaker is Dr. James Witter, of the Center for Drug Evaluation and Research at FDA, to talk on the role of animal and *in vitro* models in osteoarthritis risk reduction.

DR. WITTER: Good afternoon. I've known Lee Simon for at least 20 years, and now I've learned one of the secrets that he was involved in this trial with magnets, which attributes why he has this magnetic personality.

I've been asked--and I want to thank my colleagues at CFSAN--to tackle the issue of *in*

vitro and animal models as they relate to human osteoarthritis, a somewhat daunting task, especially considering the audience. So what I'm going to try to do today is to give you a bit of a regulatory bent on some of these issues, so you'll see some slides that look familiar, but I'll talk about them in a different way. The bottom line, no pun intended, is what I'm going to try and do is give you some food for thought here.

In particular, what I'm going to try and do is establish the kinds of like that exist to the human situation and how solid these links are. So, for example, should some of these lines be drawn with dashes? Should they be making circles? And I want to make you aware of something that we haven't really talked about yet so far. For example, when we talk about animals, I've had the privilege of working with colleagues at the Center for Veterinary Medicine here at FDA, and one of the first times I went over there and gave a presentation, because I talk also about pain and OA with that group, is they reminded me--actually

reminded me that the animals that they take care of are their patients, which is something to remember. So they actually refer to them as "companions" and the person that brings them in as "clients." So I think we need to always keep in the back of our mind the distinction, potentially, when we're referring to animals. Are they companion animals or are they animals that are used in experimental models?

Then we talk about histology cells, enzymes. What are the links, how strong are the links? And I'll wander off a bit into some discussion of surrogacy because that really is, in essence, what we're trying to get at when we talk about links.

This is a very complicated issue, as you've heard. OA sounds simple on the surface, but I think you've gotten today--and you'll probably hear it from me again--that there are more questions than answers.

About four years ago, a little over four years ago, I had the privilege of being involved in

the Osteoarthritis Initiative, and I gave one of the opening--it was, in fact, the opening presentation, and this was one of my slides that I showed right off the bat: There are currently no FDA-approved therapies that alter joint structure in OA. And that is still true today. And I think that is, in essence, also true for our animal companions, for the most part.

So the thrust of that presentation at that point in time was that this needs to be changed. We need drugs out there, we need therapies out there, and that still is the case.

So when we refer to human OA, I just want to--and you've seen some of this already. I just want to make a few points. There are some estimates out there that, you know, it has a huge economic impact. It attributes for a large number of lost work days, either due to pain or loss of function; that there are a lot of people that have this, estimates here, for example, of 12 percent. The literature in the animal sphere suggests maybe it's even 25 percent of dogs, for example, have OA.

Results, in one estimate, in upwards of half a million replacements either of knees or hips in a year or so. It's a big problem. And this was a slide that I don't know where I borrowed the number from, but it's obviously, in terms of marketing aspects, a huge market.

So what are some of the questions then that are raised in general and might be raised as we think through and think about some of these risks and links? For example, is OA an inevitable part of aging? Well, there are certain people that think that certain joints in most people remain normal way into old age. So the answer to that seems to be, at least depending on what joint you're talking about, no.

What is the etiology of OA? And it's likely, as we've heard today, multifactorial and involves genetic aspects, developmental aspects. But something I'd like to concentrate on just for a bit today are the concepts of overuse--and we get into discussions, I think, of acute and chronic trauma in that regard--and then also the issues,

amazingly, of underuse, which can be something that can lead to atrophy, which I'll talk about a bit.

Something that hasn't been discussed so far is this concept of primary or idiopathic OA versus secondary. And as it suggests, primary is the cause is unknown; secondary may be related to overuse, for example. So another feature to keep in mind as we look for these links, or lack thereof.

FDA and CDER have a draft guidance out. It was first published in 1999. Here's the website for any of you that may need it. And this guidance is, to a large part, based upon the conceptual model, I think, that Dr. Simon presented, and I'd just like to reintroduce this just to make a few extra points.

As you read the document, it's based upon the idea that, you know, biochemical changes results in structural changes, and then this pain starts to show itself, and that is, in fact, when somebody has the clinical diagnosis of OA. And it also leads to functional limitations. Dr. Simon

has pointed out reduced quality of life and potentially, in the right patient, surgical replacement. Now, these with the asterisks here are all important outcomes to any particular patient, which is then important to us, because these are something that we can give approval for for a drug, for example, if you improve these.

Which leads me then to the discussion for a bit of surrogate approval, and were you to pick out and make the mistake maybe of reading the Code of Federal Regulations, going to 314.510, you would see, as has been alluded to already, that FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled trials establishing that the drug product has an effect on a surrogate endpoint--so this is then finally referred to as the surrogate approval or Subpart H mechanism for getting on the market--that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival

or irreversible mortality. Quite a mouthful.

Again, some of this was covered by Dr. Simon, but the way that surrogate endpoint is classically defined is that it's an endpoint of a clinical trial that defines a laboratory measurement, for the most part, or a physical sign used as a substitute for something that is a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Remember those asterisks that I showed you before. The idea then is that changes in any kind of therapy on a surrogate endpoint would be expected to reflect changes in the clinical endpoint as well. This is only valid if the effect on the surrogate leads to a clinical benefit. So we struggle a lot in trying to come up and understand these relationships on the drug side.

So it's probably safe to say then that surrogate endpoints can be candidates for drug approval. There certainly are some out there. But biomarkers do not have the same regulatory implication. So a biomarker, if it's doing its job

properly, will at some point be a surrogate, but not all biomarkers are surrogates. And this slide just simply reinforces that idea that there is this overall hierarchy leading to--which is what we're most concerned about, is some kind of a clinically meaningful outcome.

So if you look at the draft guidance for OA, there is a discussion that joint space narrowing--as Dr. Simon has already discussed briefly, is that joint space narrowing is viewed as a surrogate for structural changes, whatever that means. We generally ask that the trials be at least a year in length and that you also measure pain, patient global, various kinds of patient-reported outcomes, and then the issue of whether or not structure itself can stand alone, so let me just talk about that for a bit.

Actually, it is described in the guidance that were a therapy, whatever it may be, if it were possible to actually normalize the X-ray, that that could stand along as a claim. You wouldn't need to have any other evidence. Similarly, we talk about

the fact that if you were to improve the joint space narrowing over baseline, this would also probably be a stand-alone claim because that would suggest that there was new or regrown "physiologic" cartilage. And I think there's been some discussion about normal versus abnormal cartilage in that regard.

If you were to slow the joint space narrowing by a clinically relevant amount, then we would have a discussion about whether or not there was enough evidence that you would need some symptom evidence with that and, in fact, would you need some Phase IV studies to kind of help us understand what that meant. And if you can't define what a clinically relevant amount is for us, then you would definitely have to establish some kind of a link to a clinical benefit, and that's when joint space narrowing is then functioning as a true surrogate.

So this slide, as you just saw before, I just want to make a little different twist to this. In the matrix of hyaline cartilage--in particular,

this is hyaline cartilage--a lot of the thinking has revolved, at least as I understand it, that there's an important distinction to be made between collagen and the surrounding matrix in the sense that using this building as an analogy, were one to go at the drywall, for example, the walls, you could easily patch that if there was a problem. But were you to start taking down some of the actual steel beams and supporting structure, that's an entirely different issue. And so I think part of the discussion that we always keep in mind is, you know, what are we talking about here? Are we looking at something where the Type II collagen, for example, has been altered, and maybe irreversibly altered, versus looking at proteoglycans and glycosaminoglycans.

I won't belabor on this slide anymore. It's been discussed. I just want to make a point or two here. As you look down, I've just listed that, as we all know, the hemo cartilage is primarily water. Chondrocytes swim, in essence, in this kind of water with matrix. The matrix

consists of several different things. One of the things that has always impressed me is, for example, looking at glycosaminoglycans is chondroitin sulfate, the 4 versus 6 positioning on the sulfate. And when I was doing one of my post-docs with Robin Poole up at the Shriner's Hospital in Montreal, we were raising monoclonal antibodies, and it always impressed me how an antibody, how the body could pick out a 4 versus a 6 sulfation pattern exquisitely, I think pointing out the complications and the intricacies of what goes on at all levels.

So you have, again, seen this slide, and I just want to re-emphasize the point that cartilage, particularly hyaline cartilage, is really thought to be aneural, avascular, and alymphatic. So even if it's broken, it probably can't hurt. And so that brings us, as we've matured, I think, over the last couple of years, that the joint really should be viewed properly more as an organ and not just looking at hyaline cartilage, for example.

So let me just talk for a bit about some

of the issues surrounding joint space narrowing from the human perspective that might help you understand some of the other--the animal setting, for example, and there's been allusions to this, but let me just talk about it for a bit.

When you take X-rays of knees, there are various things that you can do, and one of the things that you can do is just stand there, as you see in the first slide, extended, and that has been how some trials in the past have been done and criticized for that. So there's been a major effort over the years to try and standardize taking an X-ray. It seems pretty obvious, but it's actually quite challenging.

One of those is the middle one, which says semi-flexed fluoroscopy, so in this instance, what you do is have the patient stand there and you use fluoroscopic techniques to actually position the joint, in particular, the posterior to anterior medial aspect of the tibia plateau so that it's parallel to the beam. And there has been an immense amount of work that's been done to

standardize this. So even taking something as simple as an X-ray isn't that easy. Imagine doing this in an animal.

So there are, as I have been discussing, issues in terms of standardization for X-rays, the idea that conventional X-rays are not reproducible, so the solution has been this Buckland-Wright technique, which I've just been describing, where you, in fact, can use magnification and use software to kind of analyze these things. But when you think about it, it actually kind of creates another issue. Yes, you have been very diligent in producing some results, but now can you reproduce these in the clinic? How many clinics take the time with patients to actually go through this procedure to find out who would be a candidate to take the therapy, whatever the therapy may be? So it's an interesting conundrum.

So let's turn to *in vitro* considerations, the topic that I was asked to talk about. And I won't dwell on this too long because I'm sensitive to time. But, you know, if you're going to do an

in vitro approach, there are certain very important considerations. We've heard that the chondrocyte is a very important cell. It's an often overlooked cell. It's kind of maybe the Rodney Dangerfield of, you know, "no respect" kind of cells. But it has a very important job. It maintains its matrix. It has to respond to its environment. It has to keep things in an equilibrium. And so it's very sensitive to feedback because it has to go through anabolic phases to produce proteoglycans and glycosaminoglycans, for example; it has to destroy its environment, so it has to go through catabolic phases, where it secretes things like matrix metalloproteinases, which I'll talk about in a bit.

These ideas are what have been used for a long time, but not as successfully as many would like, to kind of get at the issue of can we use what happens to the chondrocyte as it's responding to tell, number, one, what's going on. Is it in a catabolic or an anabolic phase? And do we change that with therapy? Are we getting, for example, more anabolic responses with something?

Then the *in vitro*, whatever the situation is, has to really, you know, kind of address the issues of cell-cell contact, cell-matrix interactions. It should really talk about, you know, and address the issues of loading stresses because, as we've heard, that's one of the ways that joints get their nutrition. It's by the constant loading and unloading as we walk along so it doesn't have its own blood supply. That needs to be taken into account. And even something as seemingly innocuous as temperature, for example, you know, core body temperature is 37, but there are estimates that at the ankle joint the temperature is 29 degrees. So what was the temperature where these *in vitro* systems were conducted?

So I'd just like to take one instance here, and I've kind of put together an *in vitro* and an animal with something that was in Biochemical Journal last year and just simply summarize some of the results which I think raise some of the issues which we're discussing today.

They point out in this paper that without glucose, glucosamine can certainly act as a sole source of glycosaminoglycans for the cell. But they go on to point out that when they add glucose to their system, it acts as a strong competitive inhibitor to the utilization of glucosamine to produce glycosaminoglycans, which is a problem. So you have to figure out how much glucose then do you have versus how much glycosaminoglycan in whatever system you have.

When you look at the glucosamine itself, these particular authors found that it didn't really stimulate production of GAGs. In fact, at the higher concentrations, it seemed to actually produce less GAGs, which seems to be a paradoxical result, but as we deal with surrogates on the drug side, we've certainly seen that certain surrogates do not do what they're supposed to do. In fact, some surrogates are dead wrong. But that's where the clinical trials can come in and help answer that.

So this particular paper goes on and

discusses issues about, you know, what are the likely levels of glucose or glucosamine in an environment and, you know, how can things get there. It has to go through--you know, the best way to a joint is through the mouth. So it has to go through the stomach, bloodstream, synovial fluid. You know, is it even feasible that things can happen? We've heard a bit of that discussion today. But I think what this does is points out some of the cautions that we need to always have in the back of our mind as we interpret *in vitro* results as they might apply to a human situation.

Turning then to animal model considerations, I'd like to focus for a bit on the issue of pain because, as we heard about, pain is what really makes the human OA what it is versus just some structural changes. But it's also very important for animals, and I'll talk about that in a second.

Other considerations are the various interventions which I'll talk about; the species differences, does the animal walk on four versus

two legs; differences in biochemistry; and then differences in underuse, which I'll talk about in a bit more detail.

So, pain. It's a four-letter word. We spent two days talking about this, almost two years ago already--I'm amazed. It took that long, and we could have talked easily for two more days. Pain is a very, very complicated topic, and I'm in the Division of Analgesics, so I can attest that it's complicated.

Now, when we talk about pain in terms of humans, one of the things that's very important, I think, to remember is that in human OA pain is studied and addressed and discussed directly by the patient. You ask the patient and they tell you. And we have, as you've seen--and I'll talk about a bit more--we utilize, for example, the WOMAC for lower extremities.

In an animal setting, however, this has to be done indirectly, and quite often it's done by veterinarians, for example. So in a chronic setting, they might look for lameness, which is an

issue looking at function. Or in a more acute setting, they might look, for example, is the animal vocalizing? What are his or her behaviors? Eating, activity level? And, in fact, they even talk about physiologic changes that may occurs in terms of, for example, pulse or blood pressure. But this is a very important distinction because it's difficult to get at the issue of pain then because you can't get at it directly.

So were you to come to our division and you wanted to be approved for the treatment of osteoarthritis for treatment of signs and symptoms, we would ask you to look at the following three co-primary endpoints: pain, a functional assessment, a patient global. And we would ask that these trials be done at least for three months.

We would encourage you to employ the WOMAC pain index. As you can see here, it has pain--it's not just a simple question, How is your pain? It's actually five questions, and as you can see, they ask different kinds of questions: pain walking on a flat surface versus pain lying versus pain

standing and at night. And I think this gives us a richer idea because we still don't understand in terms of what causes directly pain in any particular joint. This gives us a bit of a more robust assessment to what's going on when somebody says they have pain.

Now, turning then directly to the animal models, I just made a few slides to list a few things here to make some points. So there are, for example, chemically induced models where you intra-articularly inject things like iodoacetate or enzymes like papain, chymopapain or collagenase. What you're really trying to do here and I think the thinking has been to create some kind of a toxic situation to the cell. You may induce, for example, some kind of inflammation. You're trying to set up a system that you can study. I think that there is a general movement away from these kinds of setting recently because they are, to some extent, maybe not really very reproducible and don't really tell us much about the situation either in humans or animals.

There are then more--the models that have been studied in a bit more detail, as far as I can see, are those that are physically induced: the anterior cruciate ligament transection model, for example, using either one or both knees in the dog or the rabbit--Dr. Altman had talked about this, for example--or the meniscectomy models in the rabbit and guinea pig; immobilization in rabbit or dog; or the patellar contusion model in rabbits. I'll talk a bit more about one of these in just a second.

Then there is something here that I have listed as spontaneous models of OA, and this seems to be where things are generally going in the field because it maybe mirrors better the situations that we're dealing with today. So, for example, the Hartley guinea pig many feel gets at the issues of age and obesity better, and then what I've listed here as genetic approaches. There are some that have been studied that have unidentified genetic defects, whereas others have been actually targeted in, for example, in Type II and Type IX collagen.

And then I guess I would argue that the hip dysplasia in dog is also a genetic model because it seems to follow in more pure-bred versus mixed-bred animals. Again, I think this is really where these animal models are going these days.

So let's just talk for a second about the cruciate-deficient dog model and some of the lessons that we seem to have learned from this setting. One of those is that chondrocytes can repair their damage, as we've heard about, and this leads to hypertrophic cartilage with increased glycosaminoglycans. This seems to be true in humans, in rabbits, and in Rhesus monkeys, for example. There is also this idea of what's been called neurogenic acceleration where you take and you actually do a dorsal route ganglionectomy, for example, to accelerate the damage so that you get more observable damage during your trial period. But there are many that feel this is not a good representation for, again, consideration of a primary or idiopathic OA. And some of the arguments go that, you know, the homeostatic phase

of this hypertrophic repair, if you use just the neurogenic acceleration versus just a cruciate ligament it's different. So you're really looking at kind of different things, and it's hard to make comparisons.

Then as I talked about and alluded to earlier, the importance of periarticular muscle, if you immobilize the joint, this can lead to atrophic changes of glycosaminoglycans. To what extent this may mimic, for example, what Dr. Brandt often talks about is quadriceps weakness in elderly women and that, in fact, this may be in and of itself a predisposing condition to human OA, not a result of.

So I'd just like to give a short example here of something. This is just such a colorful slide, I couldn't, you know, not put it in. It just points out--this is a slide showing the various domains of the matrix metalloproteinase family. It's not meant to be complete. It's just meant to show that there are several members to this family. And so there have been efforts over

the years to go after this as a target with evidence, for example, that MMP inhibitors in osteoarthritis, they hydrolyze the relevant kind of substances that we've been talking about, for example, the proteoglycans and such, that they're upregulated by disease mediators, such as we hear Dr. Abramson in the interleukin-1, for example; that if you look into *in situ* hybridization techniques and immunofluorescence, it seems to be at the right place where degeneration is occurring; that you can get actually characteristic signature cleavage fragments *in vivo* that can represent this dichotomy I was talking about before of anabolism versus catabolism; and that these are blocked by natural compounds, for example, TMPs, but also by selective inhibitors.

So one of the things that is important, again, to remember is that we're not all the same, we differ. And as you look, for example, here, under Collagenase 1, I just listed that as far as I know--and I would love to be correct, but as far as I know, there are no similar enzymes in the rodent

model of a rat or mouse. So there are always some differences between species and humans to be paying attention to.

There was a trial, some trials a few years ago where they were looking and utilizing the rabbit meniscectomy model with therapy which I've just anonymized here as Therapy X, and it has three different concentrations. And they had various parameters that they were looking at: fibrillation, fissures, erosions, and global scores. And they did the proper kind of experiment with normal and a sham and then a vehicle control. And as you can see, as you look particularly look under the 10 mg/kg/day group, some of the changes from the vehicle, for example, appear to be quite dramatic, and, in fact, some of those have reached significance, as I've indicated here.

If you look in another model, in the dog cruciotomy, again, with the same low dose and high dose of this particular therapy, as you look either at the area of the lesion or a composite assessment of the lesion, again, the data certainly suggests

that at the high dose there is some improvement here.

Well, unfortunately, these haven't all panned out. The idea is that, you know, when you talk about OA and structure modifiers, the idea is that you can limit joint damage. And I think it's pretty safe to say at this point in time, at least in human OA, when we look at things like MMP inhibitors, for example, there's no demonstrated effect in RA or OA. Some of these in the literature, these trials have been stopped because of safety concerns. And, interestingly, some of the problems have related to somewhat unexpected findings in terms of stiffness and pain in things like shoulders and hands.

Looking at bone, for example, there were some discussions briefly here already about bisphosphonates, and there have been some suggestions in Phase II trials that they could be effective, but at the most recent ACR meetings, the Phase III trials were not shown to substantiate this. So my original slide back in 2000 is still

true.

So as I end here, I'd just like to bring up a few points that might be of use for your consideration, and I've drawn a comparison here between RA and OA.

In RA, we have many new compounds that have entered the market, and they have demonstrated either a clinical benefit before or after drug approval and structural benefit before approval. And some of the clinical benefits that have come later has been looking at longer-term, more robust endpoints, such as patient's function, for example.

In OA, as I said before, we have currently in the human setting only drugs for a clinical benefit, meaning pain reduction, for example. So were we to look then at structure modifiers, how do we approach this? When, for example, if we look at a clinical benefit alone, would we want that to correlate with a structural benefit, before or after therapy? And that is, in fact, where the discussion has come in in terms of looking at these compounds for what might be a Subpart H type of

approval.

Now, I think there's been a lot of learning that has gone on over the years about joint space narrowing, and I think we continue to learn. I've just illustrated here something to think about. For example, I think not too long ago, it might have been fairly straightforward and agreed to that there's a trajectory here for somebody who demonstrates rapid loss of joint space narrowing versus somebody who's on this kind of trajectory, which is slow. But, in fact, it may be that it isn't quite so simple and that, in fact, in any individual patient it may be that it's a combination of these two features. So that, for example, somebody may be on a rapid course for a while, and as we've heard, the body attempts to make some repairs and, in fact, is successful. But then things pick up again. And as you think this through, whenever you might take a snapshot with your X-ray looking at joint space narrowing, one has to always consider how much this might factor into the results that you get, or lack of results.

One of the ways that we've struggled with this issue about what should be the endpoint is to try and come up with something called the virtual joint replacement endpoint in OA. And this is really an effort to kind of standardize development because we're sensitive to the fact that not all health care systems across the country and across the world are the same. So we've been wondering with colleagues if we could come up with an agreed-to standard, a composite endpoint, for example, of pain function and radiographic endpoints, that might allow us to look at the time to a virtual endpoint of joint replacement, again, getting at this idea of function and--I'm sorry, of survival as an important endpoint in OA.

So just to wrap up, I think we've gotten a lot of instances here that osteoarthritis is considered nowadays to be an organ. It's a very complicated organ and much to be learned, but as we look through here, you'll notice that I've drawn--everything else has an arrow, for example, going to pain except cartilage. So whatever happens in

cartilage seems to act indirectly through other mechanisms to lead to pain, which then leads to these other clinically important features. Somewhere down here versus somewhere up here there's a transition from a biomarker to a surrogate as it becomes more looking like a clinical endpoint. And then we wrestle, along with a lot of others, in terms of where can we actually demonstrate these kinds of relationships, these links, as I've talked about before, and establish those. Is it in Phase I, II, or even Phase IV trials?

I'd just like to end with part of a sentence from a recent paper from Dr. Brandt. Although he was talking for the most part about therapies, I think this is useful for our discussions today. He says that, "The validation of a molecular target in human disease can be obtained only after positive results are obtained in Phase II clinical trials in humans." So I guess maybe the only way that we really can hit the mark is to study the mark.

Thank you.

DR. MILLER: Comments or questions?

DR. ABRAMSON: Steve Abramson. Jim, I'm just curious about this surrogate endpoint, the H. Apropos of Ken Brandt's comment, which I think was very important, do you envision that there will ever be a surrogate marker where there hasn't been good data, at least with a preceding medication for Phase III effects on that surrogate marker? I'm thinking of serological tests in lupus as an--I'm just trying to think of ways that one can justify using a surrogate marker when there has not been good data affecting that marker, gives a good clinical outcome.

DR. WITTER: Are you asking just in general terms?

DR. ABRAMSON: I'm curious about this H pathway, especially after all the discussion on structure modification in osteoarthritis where there has always been the notion, at least up until now, about needing to have some symptom benefits.

DR. WITTER: Right, right. The essence of

a Subpart H approach is that at some point in time you will have to demonstrate that there is some clinical benefit, whatever that may be. And we have not specified necessarily what that clinical benefit has to be, for example, if it's pain, if it's improved function, if it's time to less need for joint replacements, for example. But the idea of surrogates is that you could be approved, on the market, but validation of that surrogate endpoint would have to then come with due diligence, with adequate and well-controlled trials. There are caveats here that, you know, a Subpart H track, for example, might be viewed in simplistic ways as a quick way to get on the market, but it also is a quick way to get off the market if things aren't validated.

I don't know if that answers your question or not.

DR. MILLER: Other comments or questions? Dr. Lund?

DR. LUND: Just to show my ignorance here, nobody has mentioned TMJ. Is there anything in

this having to do with jaw and jaw diseases?

DR. WITTER: Well, I actually work with Ray Dionne, who is the Dental Institute here at NIH, and we often wander into the discussion of TMJ. It's a very complicated setting, as you might imagine, and there has been a lot of renewed interest to look at that as a useful model for OA in general. So it has not been overlooked, though.

DR. MILLER: Dr. Harris?

DR. HARRIS: I'm not quite sure how to phrase this question to you, but it's just something that is very confusing to me, and that is, when we are talking about the biosynthesis now of the whole matrix component, we're talking about many different factors, including the collagen Type II and then those glycosaminoglycans that you mentioned the chondrocytes are able to make. But do we have any evidence that once we destroy the collagen we're able to reconstruct the matrix? And could that be an irreversible step here?

DR. WITTER: We have colleagues in the room that can answer that as well, but my general

understanding of the literature is that that is the case, that once collagen begins that cascade, that is the beginning of the end for that joint.

DR. LUND: Does that mean it cannot be repaired or reversed?

DR. WITTER: In repair or reverse, yes, I think that's generally a fair statement. And then I think--was it Dr. Lane who had brought it up before?--this idea of the repair aspects may not then be the right kind of collagen, that it can't withstand the stresses and such. So, you know, it's--the term has become important. Although it may be repaired, it may not be the right kind of collagen. It's not laid down properly. It doesn't function properly.

DR. MILLER: Jean?

MS. HALLORAN: We heard that crystalline glucosamine is approved as a prescription drug for treatment of arthritis in Europe. Is there a reason why it hasn't been approved in the United States or can you comment on that?

DR. WITTER: Probably not. I'd better

not. There are others that can comment. I won't.

DR. MILLER: Okay. Thank you.

We'll take a break for 15 minutes. Be back here at 3:15.

[Recess.]

DR. MILLER: For the remainder of this afternoon, we're going to deal with an open meeting, open public hearing. Individuals who wanted to make statements to the committee are invited to do so, having made a request to the FDA prior to this meeting. We have five such requests, and we will have these individuals in just a moment. But I have been asked to read this statement prior to the meeting concerning the openness of the hearing.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an

individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or group that's likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group's payments of your travel, lodging, and other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first presenter is Dr. Jason Theodosakis of Cargill. Dr. Theodosakis, you have seven minutes.

DR. THEODOSAKIS: Thank you very much. I'm not with Cargill. They paid for my trip here. I'm not an employee of Cargill.

Here are my disclosures. I'm hoping to have a second page because the more you have, the less biased you are.

I think the presentations have been excellent this morning. I would have changed my presentation based on what has been presented so far, but basically I think osteoarthritis is underestimated. This is a recent radiographic study on 55-year-olds and older, mostly women, and they found 96 percent had radiographic evidence. So OA is real common. CDC keeps upgrading the percentages in the public, and as we get fatter and more diabetic and older, I'm sure this is going to increase.

Our current treatment of NSAIDs are not disease-modifying, and, in fact, as more and more evidence comes out, the treatment with NSAIDs appears to be more and more toxic, leading to blood pressure, congestive heart failure, and possibly an acceleration of the disease.

Often, people quote the Singh study that says 16,500 people a year are dying from

complications from NSAIDs, but this was published back in '98. And if you look at the assumptions, we have new evidence to say that this number, which is 45 deaths a day, may actually be quite a bit higher, especially since we found an interaction, for instance, between Ibuprofen and aspirin that may reduce the cardioprotective effect of aspirin, as well as many other issues. So I think the need for this conference is very timely, and I'm glad that everybody is putting so much effort into it.

The other thing that I saw today is that this is such a variable disease and so difficult to study that we really should look at all the data. And I'm not sure if I agree, but just looking at Phase III clinical trials, because we have indirect measures and there's all kinds of problems with the study which have been well delineated. But if you look at the whole data, that's the way to make the decision. It could be argued even that animal data looking at gross and histologic and grading the cartilage before and after treatment with the supplements might be a more precise measure of

what's happening with the supplements rather than the indirect surrogate measure of pain and function scales or even X-ray.

The outcome measures are real interesting as well, and there are three studies that I've noticed with chondroitin, for instance, that say, Hey, what does this do to society? If in France we give chondroitin to people, how does this affect cost? How does this affect NSAID consumption? And the outcome measures are also important. This particular study of 11,000 patient records found that 50 percent of the people that were using NSAIDs for osteoarthritis were able to stop completely on 1200 mg of chondroitin, and the average reduction was 67 percent. And even though chondroitin is expensive, the net cost was zero because there was decreased physical therapy visits, complications related to NSAIDS and so forth. And I believe there are two other studies that have even better evidence to show that there's a cost savings.

There's some talk about glucosamine

sulfate versus glucosamine hydrochloride, and the issues I wanted to bring up are the following: these are salts, and the salts break apart in the small intestine with a high pH; you have an uncharged molecule that then can pass through membranes easily, and this is probably what gets to the chondrocytes where all the action occurs. Some of the early basic science and even the pharmacokinetic data was done with radiolabeled glucosamine hydrochloride. And there are essentially two studies now that I've noted that have a comparison between HCL and sulfate, and when corrected for molecular weight, they were equivalent in proteoglycan synthesis. Interestingly, the N-acetyl-glucosamine was not as effective.

Another study suggested--this is a basic science study on equine cartilage explants--that it is indeed the glucosamine and not the sulfate that is the active component, and glucosamine sulfate and hydrochloride were similar in terms of the outcome measures in basic science experiments.

Other people point to the negative studies on glucosamine HCL and say, Hey, we have these negative studies, that means glucosamine sulfate is probably more important. But these studies really have to be looked at with a grain of salt. One study was very short, eight weeks in duration. The subjects in the study had a higher level of more advanced disease, Grade 4 K&L. And they were allowed to take NSAIDs ad lib, and so it's sort of like doing a study on Advil when the people are allowed to take Aleve with it. You know, we should be careful in reviewing those negative studies.

A study by Lou Lippiello looked at animal histology in rabbits and found that indeed glucosamine hydrochloride and chondroitin sulfate both were effective at reducing the lesions in the rabbits histologically when pre-treated, and the combination had a better effect than either one alone.

With chondroitin, the effective dose, several studies now show 800 mg. People have said that, well, it's probably not absorbed so it

couldn't be effective. But there have been pharmacokinetic studies with it, and you have to look at all the double-blinded studies. They're all positive, in addition to the outcome study which I earlier alluded to.

The largest study so far, disease-modifying with either supplement, is 800 mg of chondroitin sulfate, and this showed not only a significant difference between the placebo but minimal joint space actually significantly increased in the chondroitin group over a period of two years using flexed X-ray positioning guidelines.

In summary, I think we look at all these studies and we have to realize some key points. You need all of the evidence, not just the placebo-controlled trials, because of the heterogeneity of the disease and all the implications in doing the research. And we are studying people with primary OA, and the folks out in the public have a lot of secondary OA. I haven't seen any studies of this, but clinically I've seen the most dramatic response

in people with crystalline disease, pseudogout and gout. You know, it would be great to look at this.

Glucosamine hydrochloride and glucosamine sulfate and chondroitin sulfate I think would be a big benefit to the public in reducing overall morbidity and mortality from our current treatments and reduce the costs overall of treating osteoarthritis in society.

Thank you very much.

DR. MILLER: We have time for one or two questions.

[No response.]

DR. MILLER: If not, thank you.

The next speaker is Dr. Gayle E. Lester of NIH. You have seven minutes, Dr. Lester.

DR. LESTER: Thank you. I appreciate the opportunity to come to speak today, and I have just a few comments to make initially about some of the problems associated with the extrapolation of data generated from animal models to human disease.

Dr. Witter has really covered this very extensively in his presentation and has described

for you the numerous animal models of OA that exist, and these include both spontaneous and induced disease.

While these models present opportunities to explore changes in articular cartilage and associated joint structures, each one has its strengths and weaknesses. Many agents show protective effects in animal models, but the predictive value for human OA remains somewhat obscure.

Whether or not these models accurately reflect disease risk factors sufficiently to indicate prevention and prophylactic actions of agents really remains to be shown.

In an effort to identify better biomarkers for OA to help facilitate clinical trials and drug development and drug discovery, the NIH has recently launched a large clinical cohort study that I'm going to spend the rest of my time talking about today.

The study has been referred to several times this morning, and I appreciate the