UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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IMMUNOLOGY DEVICES PANEL

+ + +

November 14, 2019
8:00 a.m.

DoubleTree by Hilton
Washington DC North/Gaithersburg
620 Perry Parkway
Gaithersburg, MD 20877

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SCOTT BURCHIEL, Ph.D.	Temporary Non-Voting Member
YIMING LI, D.D.S., Ph.D.	Temporary Non-Voting Member
JOHN SUZUKI, Ph.D., D.D.S.	Temporary Non-Voting Member
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RICHARD BURTON, D.D.S.	Temporary Non-Voting Member
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M E E T I N G

(8:02 a.m.)

DR. RAO: Okay. Good morning, everyone, and welcome back.

I would like to call this meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee to order.

My name is Raj Rao. I'm Chair of this Panel. I'm an orthopedic spine surgeon, professor, and Chair of the Department of Orthopedic Surgery at George Washington University.

I note for the record the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

Today is the second day of this Public Advisory Panel Meeting. The focus of this 2-day meeting is to deliberate the topic of immunological responses to metal-containing products regulated as medical devices. The discussion will focus on metal-containing implants as well as dental amalgam.

FDA is convening this Committee to promote an open public discussion of and seek expert opinion on currently available scientific and clinical data pertaining to the biological responses to metal implants and dental amalgam, and the potential associated sequelae. Today during the first half of the day, we will begin with the Open Public Hearing of this Advisory Panel meeting.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves once again. Please state your name, your area of expertise, your position, and affiliation. And let me begin with Dr. Christian on that side of the table.

DR. CHRISTIAN: Thank you. Good morning. Industry Rep Whitney Christian,

molecular toxicologist, expertise in toxicology and biocompatibility.

MR. LISON: Good morning. Wyatt Lison. I'm a partner with Feinstein, Doyle, Payne & Kravec. I am the Consumer Representative, and I'm a consumer lawyer.

MR. O'BRIEN: I'm Joe O'Brien. I'm President and CEO of the National Scoliosis Foundation. I am a patient with cardiac, spinal, and gastrointestinal devices implanted, and I am the Patient Representative.

DR. SUZUKI: I'm Jon Suzuki, Professor Emeritus, Temple University, Philadelphia, Departments of Periodontology and Oral Implantology, and also Department of Microbiology and Immunology.

DR. BADYLAK: Morning. I'm Steve Badylak. I'm a Professor of Surgery at the University of Pittsburgh Medical Center, and my area of interest has been a patient response to implanted biomaterials.

DR. BURCHIEL: Good morning. My name is Scott Burchiel. I'm also a Distinguished Emeritus Professor. Has me listed as a regular professor on the program, but I am a immunologist, pharmacologist, and toxicologist and have worked in the area of immunotoxicology for many years.

DR. WEISMAN: Good morning. My name is Michael Weisman. I'm a rheumatologist by training, and I sit in the Distinguished Professor of Medicine row over here, and I'm from UCLA School of Medicine and Cedars-Sinai Medical School, and my specific interest is in environmental and genetic risks for outcome in chronic rheumatic diseases.

DR. JANNETTO: Good morning. My name is Paul Jannetto, and I am a clinical chemist. I am a consultant and laboratory director of the metals laboratory at Mayo Clinic. My expertise is in toxicology, therapeutic drug monitoring, and elemental analysis.

DR. PARKS: Good morning. My name is Christine Parks. I'm an epidemiologist at

the National Institutes of Health. My expertise is in designing and conducting research on environmental and occupational risk factors for systemic autoimmune diseases and preclinical autoimmunity.

DR. TAYLOR: Hello. My name is Jim Taylor. I'm a dermatologist at the Cleveland Clinic Dermatology Plastic Surgery Institute and the Cleveland Clinic Lerner College of Medicine. I used to work for NIOSH many years ago, so I have an interest in occupational and environmental dermatology and dermatologic allergy, also quality of patient safety outcomes, and also dermatologic allergy and contact dermatitis if I didn't say that. Thank you.

DR. LEMONS: Jack Lemons, University System Professor Emeritus at the University of Alabama Birmingham, sharing time equally between dental materials and mechanics, clinical dentistry, biomedical engineering and orthopedic surgery. My area of expertise is biomaterials and biomechanics and, in recent years, focusing on consensus standards related device products.

DR. LI: My name is Yiming Li, Distinguished Professor for Restorative Dentistry at Loma Linda University School of Dentistry. Also, Associate Dean for Research. I'm also a Professor of Microbiology and Molecular Genetics at the Loma Linda University School of Medicine. My research interest includes biocompatibility and toxicology of dental materials and products.

DR. POLLARD: Good morning. I'm Michael Pollard. I'm a Professor in the Department of Molecular Medicine, Scripps Research Institute in California. My major interest is autoimmunity and the role of various environmental exposures in autoimmune disease.

MS. ASEFA: Hi, my name is Aden Asefa, and I'm the Designated Federal Officer for this meeting.

DR. BURTON: I'm Richard Burton. I'm from the University of Iowa. I'm a Professor of Oral Maxillofacial Surgery, specialize in pediatrics. My area of expertise is in dental implants and implantable craniofacial devices.

DR. DYKEWICZ: I'm Mark Dykewicz at St. Louis University, where I am Professor of Internal Medicine and Chief of Allergy and Immunology. I evaluate patients with suspected metal hypersensitivity and care for them. I've also spent a considerable amount of my career developing patient care guidelines.

DR. GERMOLEC: Good morning. I'm Dori Germolec. I'm with the National Institute of Environmental Health Sciences. I'm a toxicologist, and my area of expertise is looking at the effects of environmental factors on the immune system.

DR. JACOBS: Good morning. I'm Joshua Jacobs. I'm an adult reconstructive orthopedic surgeon and Professor and Chairman of Orthopedic Surgery at Rush University Medical Center, where I also have the title of Vice Provost for Research at Rush University. I'm also an Adjunct Professor of Material Science at Northwestern University, and my interest is in biomaterials and biocompatibility of permanent metal devices.

DR. McDIARMID: Good morning. I'm Melissa McDiarmid. I always get this reverb, so I don't know if that's because I'm in a corner or what -- somebody's -- oh, it's like a vortex here. I'm Professor of Medicine and Epidemiology and Public Health. I am a clinical toxicologist. And the reason I'm here is I direct the Department of Veterans Affairs depleted uranium and embedded fragment program, which is medical management for IED-injured veterans.

DR. CONNOR: I'm Jason Connor, biostatistician for ConfluenceStat and Assistant Professor of Medical Education at University of Central Florida, College of Medicine.

DR. BABENSEE: I'm Julia Babensee from Georgia Tech and Emory University in the Department of Biomedical Engineering, and my interests are in biocompatibility, host

responses to materials, and immunomodulation.

DR. GIORI: I'm Nick Giori. I'm an orthopedic surgeon specializing in joint replacement surgery from Stanford University and the Chief of Orthopedic Surgery at the Palo Alto VA.

DR. ZUNIGA: Good morning. I'm John Zuniga. I'm an oral maxillary surgeon, Chief of the Division of Oral Maxillary Surgery in the Department of Surgery and Professor in the Department of Surgery and Neurology and Neurotherapeutics. I'm a practicing clinician as well as interest in oral facial trigeminal nerve disorders and acute and chronic facial pain.

DR. ADJODHA: Good morning. I'm Mike Adjodha. I'm currently Acting Assistant Director for Restorative and Surgical Dental Devices team in FDA's Division of Dental Devices.

DR. YUSTEIN: Aron Yustein, Assistant Director, Office of Product Evaluation and Quality, CDRH, at FDA.

DR. FISHER: Good morning. Ben Fisher, Director of the Office of Health Technologies 3, overseeing Gastro-Renal OB/GYN, General Hospital and Neurologic Devices within CDRH at FDA. Area of expertise, developmental genetics and developmental reproductive toxicology.

DR. RAO: Thank you all. It's very clear that there's a wealth of experience and knowledge amongst the members of this Panel and also in the audience. So hopefully we'll have a robust discussion as we move forward to the Panel Deliberations time, and then I'll ask each of you for your individual inputs as we move forward to responding to the questions that the FDA has for us.

For topics being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views

without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a productive meeting.

Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of this meeting room.

Ms. Aden Asefa, the Designated Federal Officer for the Immunology Devices Panel, will now make some introductory remarks.

MS. ASEFA: I will now read the FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations. The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been

screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss the topic of immunological responses to metal-containing products regulated as medical devices. The discussion will focus on metal-containing implants as well as dental amalgams. Implants are medical devices that are placed into surgically or naturally formed opening of the human body and are intended to remain there after the procedure for an extended period of time, typically greater than 30 days.

While not considered an implant, dental amalgam is included in this discussion today because it is a patient for patient and user exposure of mercury compounds and some purported similarities in the adverse biological responses and clinical manifestations elicited by some dental amalgams up to that of traditional metal implants.

Based on the agenda for today's meeting and all financial interests reported by the Committee members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Stephen Badylak and Dr. Joshua Jacobs.

Dr. Badylak's waiver addresses his imputed employer's research contract from a firm that manufactures an implantable metal device. Dr. Badylak's employer is awarded between $50,000 and $100,000 under the agreement. As a principal investigator for this study, Dr. Badylak receives between 1,000 and 5,000 in salary support.

Dr. Jacobs's waiver addresses his employer research grant from a firm that manufacturers an implantable metal medical device -- I'm sorry -- metal device. Dr. Jacobs's employer is being awarded between $100,000 and 300,000 total under the

agreement. Dr. Jacobs's employer has been awarded two research grants from the National Institute of Health, which are related to the meeting topic but not to manufacturers of the implant devices. Dr. Jacobs's employer is awarded between a million and $2 million total under the grants.

Dr. Jacobs served as an expert witness in two lawsuits which address a matter that is relevant to the general issues coming before the Panel. His current compensation for service in these cases is zero dollars, but compensation is expected to be between 20,000 and $50,000 in the next 12 month.

Dr. Jacobs is identified as a co-inventor of three products that are related to general issues coming before the Panel. Dr. Jacobs and his employer are entitled to revenue if the patents are approved and licensed, but they do not currently generate any revenue.

These waivers allow these individuals to participate fully in the Committee deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website. Copies of the waivers may also be obtained by submitting a written request to the Agency's Division of Freedom of Information.

Dr. Whitney Christian is serving as the Industry Representative, acting on behalf of all related industry, and Dr. Christian is employed by Medtronic. For the record, Dr. Raj Rao is serving as a temporary Chairperson for the duration of the meeting.

We would like to remind members and consultants that if the discussions involved any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the Panel of any financial relationships that they may have with any

firms at any issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript.

Thank you.

Before I turn the meeting back to Dr. Raj, I would like to make a few general announcements.

Transcripts of today's meeting will be available from the Free State Court Reporting.

Information on purchasing videos of today's meeting and handouts for today's presentation are available at the registration table outside the meeting room.

The FDA Press Contact for today's meeting is Michael Felberbaum and Angela Stark.

All written comments received were provided to the Panel and the FDA review team for their review prior to today's meeting. There is an active docket where members of the public can pose written comments. The link can be found on the FDA website and in the registration table.

I would like to remind everyone that members of the public and the press are not permitted to the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing Session and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself in every time you speak.

Finally, please silence your cell phones and other electronic devices. Thank you.

Dr. Rao?

DR. RAO: Thank you. We will now proceed with the Open Public Hearing of this Advisory Panel Meeting. For the record, all Panel members have been provided written comments received prior to this meeting for their consideration. During the Open Public Hearing, public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Aden Asefa will now read the Open Public Hearing Disclosure Process Statement.

MS. ASEFA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing Session of the Public Advisory Panel, FDA believes that it is important to understand the context of the individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written and oral statement to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance to 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 this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. RAO: Before we start, however, I wanted to remind you of what was mentioned yesterday. The FDA received a large number of requests by members of the public to speak during this 2-day meeting and attempted to accommodate all individual time requests. However, due to the large number of individuals who signed up, most speakers could not be granted the full amount of time that they requested.

During the Open Public Sessions, you will see that different speakers are allotted different amounts of time. People who requested to speak indicated that they wished to speak for 3 minutes, 5 minutes, or sometimes 10 minutes or more. After considering the number of speaker requests, and the time available for the Open Public Sessions, and in order to ensure that all who requested to speak were given an opportunity to present, the FDA assigned 3 minutes of talking time to those requesting 3 minutes, 4½ minutes to those requesting 5 minutes, and 8½ minutes to those requesting 10 minutes or more.

In addition, several speakers who requested and were assigned speaking slots have subsequently asked to combine their allotted times to speak as one group. In these cases, the total time for that group was assigned based on the time originally allotted to the individual requesters. In some cases, individuals opted to yield their time to other speakers. Therefore, there is at least one instance where a series of speakers or even an individual speaker may have more than 8½ minutes.

For speakers who will be presenting today, AnnMarie Williams -- Ms. Williams, could you please stand up -- will be assisting you in terms of coming up to the podium. So please pay close attention to her instructions. As you can see, we have two podiums to minimize the amount of time between speakers, so please be ready to speak as soon as the person before you is finished.

When at the podium, we ask that each presenter speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. Your time will start once I acknowledge you by name.

Because of the number of people who are speaking today, the Panel asks that each speaker remain cognizant of their speaking time and help keep us on track. As your allotted time nears its end, I will kindly remind you of your remaining time. If your presentation begins to run over your allotted time, I will ask that you conclude your

remarks.

Although we hope that this will keep us on time, if your presentation begins to run significantly over your allotted time, the microphone will be shut off, and the next speaker will be recognized. Again, this is purely to ensure that everyone who registered to speak can be accommodated during the Open Public Session.

Will Speaker Number 1 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record. I'd like to point out that the first 12 speakers have requested that their time be combined. So the entire group as a series of speakers has been allotted 63 minutes, and I'll ask Speaker Number 1 to coordinate the transition of speakers in the group.

Thank you. Please go ahead.

MR. URAM: Very good. Thank you, Chair. Good morning, and thank you for the opportunity to comment to this distinguished Panel. My name is Eric Uram. I am a consultant to government, business, intergovernmental organizations and nonprofits on issues related to persistent bioaccumulative toxics, including mercury.

I've been a student of everything about mercury since about 1985, where I've gleaned knowledge on mercury sources, fate, transport, uses, releases, exposures, toxicity, disposal, impacts, and policy ranging from the local to the global. Over the past 18 months, I have served as the organizer for a document entitled the "Chicago Declaration to End Dental Industry Mercury Use" and worked with the Consumers for Dental Choice in that regard.

I began efforts to organize the Chicago Declaration in early 2018. It resulted in a product of 50 economic, social and environmental justice organizations, including Healthcare Without Harm, Sierra Club, Green Peace, Environmental Justice Health Alliance, the Pennsylvania State Council of Churches, the Alliance of Nurses for a Healthy

Environment, Learning Disabilities Association of America, and Physicians for Social Responsibility, to name a few. Following my comments, you will hear from about a dozen of the groups and supporters of the Declaration.

In addition to those you will hear from, the Declaration has the support of the millions of Americans who belong to those groups, all of whom recognize the many issues of concern related to mercury exposures. Their concerns begin when the mercury is mined and only end when sequestration or permanent storage takes place.

Most troubling to us all are the impacts to neurological development. Many scientific articles document mercury as a neurotoxin, including methylmercury's ability to enter the brain and disrupt development and function. The natural barriers to toxic materials prevent elemental mercury from entering but are permeable to methylmercury.

The issues FDA raises about in vivo methylation and demethylation by internal microbiomes of the mouth or digestive tract, or even the sinuses or lungs, increase our concerns. The additional immunological impacts and damages to organ function further increase the urgency to groups felt about the need to address amalgam.

All 50 groups helped draft the Declaration due to FDA's recalcitrance for requiring restrictions on amalgam placement in patients most at risk from this mercury. These patients make up subpopulations who access Federal Government dental programs, families and members of those serving in our armed forces, persons incarcerated in correctional facilities, tribal members, or economically challenged families, all of whom, FDA indicates, get the vast majority of all dental amalgam restorations, which add to the mercury problems we all face.

When used, because it is an element and cannot be destroyed, the mercury eventually is released, becoming a global pollutant that knows no barriers. Recent USGS research found that we have increased background levels of mercury by about twentyfold

since the Industrial Revolution, taken from ice cores that were harvested in the Wyoming glacial field, thousands of feet above where we normally travel and miles away from general human activity.

As a result of such evidence, nations have joined together to create an international action on mercury, resulting in the international, legally binding instrument called the Minamata Convention on Mercury. Under Minamata, language approved by all parties during negotiations, including the USA, call for the combined efforts from all parties to end purposeful uses and incidental emissions of mercury from anthropogenic sources. And that includes mercury from the dental industry.

These concerns drove us to bring these issues to the FDA mainly because leadership demonstrated by other nations who joined Minamata have moved well beyond what FDA currently recognizes as their obligation to protect citizens here from mercury. We feel the government has a responsibility to its citizens to act to protect them. Taking into consideration the currently available physically equivalent, cost-competitive, and technically superior alternative materials, solutions to using amalgam are constantly being used by dentists practicing under the same regulations as those who place amalgam.

While these materials may have a slightly higher initial cost, the cost is effectively offset by the improvements to oral health due to the minimally invasive nature of tooth repair required by these alternatives, reducing risk from exposures to mercury that can combine with other heavy metals or other toxicants to create negative outcomes, and the improved mental health of those patients knowing they do not have toxic mercury in their mouth and they have not created any additional demand for mercury.

When we started to engage these groups, all of them questioned why amalgam is still available even with this generally recognized unsafe classification. We all wondered why, based on its premise, if amalgam were brought to the FDA now as a new product,

could someone ever hope to have a product consisting of 50% mercury approved as a dental restorative material for use in the general population, especially in women who are pregnant or nursing or in still-growing pre-adolescent children.

We currently understand knowledge about the toxicity of mercury, policy signals in the Minamata Convention, technical aspects in new substitute materials, market drivers and ever-lower costs for these newer materials, and most importantly, the health implications involving neurological and immunological impacts, all signal now is the time for change.

As we request in the Chicago Declaration, FDA needs to move to restrict amalgam use in sensitive populations to protect our children and help protect the environment, which in turn will help protect us all. We recommend FDA play a more active role in protecting sensitive populations. We're encouraged by the fact FDA has chosen to include immunological issues in the assessment on whether dental amalgam policy requires change, and we see that time marches on.

In general, amalgam restorations haven't changed in over a century, while the new materials have seen marked improvements in the last decade. To make sure we avoid any regrettable substitutions along the way, FDA must play a role by assuring patients the materials used do not create a threat to health during production, use, or disposal. At a minimum, to ensure the market plays its proper role in amalgam use, FDA must develop patient materials on options related to having one material provided versus another, and end the Federal Government's preference for amalgam in all Federal programs where they provide dental care.

That concludes my remarks, and I now yield do Dr. Mark McClure, a dentist practicing mercury-free dentistry.

DR. McCLURE: Thank you for allowing us to speak in front of you. My name is

Dr. Mark McClure. I'm a practicing dentist here in the Washington, D.C. area. I have been mercury-free since 1979, and I have been associated in the past and currently with Consumer for Dental Choice.

I'm here to talk about the couple of the issues that came about in this -- from this Panel yesterday, namely, the longevity of the alternatives being one. Many recent studies verify that composites' longevity is comparable if not superior to amalgam. I'll refer you just specifically to the '07 Opdam study, which concluded, and I quote, "Life tables calculated from the data reveal a survival for composite resins of 91% at 5 years and 82% at 10 years." For amalgam, the survival is 89%, which is less, at 5 years, and 79%, which is less, at 10 years. Large composite restorations show us a higher survival in a combined population and in low risks.

Now, what I'm trying to do here is I'm trying to bring my experience and studies to the table here, because I know that we're all scientists, you know, looking at that. Based on these and other studies, the World Health Organization says recent data suggests that resin-based composites perform equally well as amalgams. The European Union Scientific Committee agrees that "recent studies from the Netherlands, Sweden, and Denmark show very good long-term clinical effectiveness of posterior resin composite restorations, with equal and better longevity than for amalgams."

The European Commission report concludes: "Given the results of recent studies comparing the longevity of different materials in the present study, it is considered that the longevity of mercury-free fillings is no longer a factor with significant effect on the overall cost difference between dental amalgam and composites, or even glass ionomers restorations," which is the other posterior resin alternative that we have.

So, in summary, studies confirm -- and of course my experience in this for the last 30 years -- confirm that alternatives are very appropriate and we don't need mercury

fillings anymore for that.

Secondly, there was a question regarding the chair time it takes to place an alternative. There have been studies timing how long it takes to place a mercury amalgam versus an alternative. For example, studies were done in Sweden before it was, of course, banned, before it banned the use, that found that the time needed to carry out a mercury-free restoration was reduced significantly, as the dentist had gained more experience in handling of the mercury-free materials, so that there is currently no or minor time difference to perform a mercury-free restoration compared to amalgams. Of course, that just makes sense. The more you use something, the better off you get at doing it. Another study found that glass ionomers, which is the other alternative posterior replacement things that we as dentists have, can be placed faster than amalgams, and that was a 19.8 minutes to the glass ionomer compared to 22 minutes for the amalgam.

It should be noted that the range of time may vary, obviously, depending on what's the difficulty of doing that is all about. If I am replacing a mercury filling as a composite, with a composite, it's going to take me longer to go through the angles and other things as if I'm replacing a composite. It's also going to be different if I'm replacing a two-surface filling versus a one-surface filling. So there's a lot of variables involved in that, which I should, you know, should mention. The summary of the chair time is that studies are finding little, if any, time difference, and that's certainly consistent with my experience.

The third issue that I want to address here is the technical difficulty in using alternatives. It's important to remember that some dentists haven't been adequately trained in using alternatives because -- and I think that there was a study done in the 1990s on, you know, looking at dental schools that said they weren't being trained in the use. However, there is not a physician or a dentist here that doesn't have a requirement for their CEUs to take continuing education to get their license.

And all I'm going to say is that in my 40 years in dentistry, there's been incredible advances. I couldn't even imagine what I'm having to practice now and what I was practicing before. So, obviously, we have to stay abreast, so I think that this is kind of a false thing here. So the problem really is not with the material. The problem is with the dental school instructions and, obviously, hopefully, the enforcement that we can put behind with the FDA. So the World Health Organization, the WHO, put it kind of cool. And that is that if we were taught composites as dentists prior to amalgams, many of us may find amalgams difficult to place.

The fourth is the risk of alternatives. Of course, that's always brought up. There's a risk with mercury. How about the risk for the alternatives? This has been extensively studied by many, and we found that there are no risks. I'll refer you to a risk assessment comparing amalgam and the alternatives released by the Healthcare Research Collaborative of the University of Illinois, Chicago School of Public Health and the Healthier Hospital Initiative and the Healthcare Without Harm. These researchers conclude there is no current evidence of significant personal or environmental toxicity from non-metal alternatives. And all of these, the footnotes of all these, where you can see the research, will be included in the written things that you'll have there.

Finally, the last issue that somebody on the Panel raised yesterday was that risk about mercury in the dental offices, and is there a risk for the people in dental offices like myself and others. And the answer, of course, is yes. Remember, mercury, as a dentist, you either choose to put it in, so there's a coming in, or you choose to take it out, or take it out, and there's vaporization in both, on the coming and going of that whole thing. So I refer you to 2004 Scottish study on the mercury vapor levels in a dental practice and the body mercury levels of dentists and controls, and which found, and I quote, 122 out of 80 operatories were tested, and they found that two-thirds of those had a series

environmental mercury measurement in one or more areas that was above the occupational exposures standard set by the health and safety executives. Obviously, this high level of mercury in the dental environment should be concerning to me as a dentist, to my assistants, to my hygienists, even to my office personnel, and anybody that enters my practice. So there is mercury hygiene for us all to learn and understand.

And I will tell you as a practicing dentist, I have a mercury vapor analyzer, and it's off the charts when you're taking a mercury filling out, so there's obviously a safe removal involved in this whole thing.

So, in conclusion, I thank you very much for giving us the time and your ear to this very important issue, and I urge the FDA to take some action against amalgam fillings. As a practicing dentist who serves a diverse community, I assure you that we have mercury-free materials and can meet the individual needs of all our patients. Thank you.

DR. MITCHELL: Good morning, Chairman Rao and members of the Committee. My name is Dr. Mark Mitchell. I have no conflicts with commercial interests.

I'm a public health and environmental health physician and co-chair of the National Medical Association's Commission on Environmental Health. The National Medical Association is an organization representing the interest of African American physicians and our patients for the last 124 years. It was formed when African American physicians were excluded from the AMA, which is a policy which continued into the 1970s. I've been involved in investigating the environmental health effects of general amalgam and amalgam policy for more than 15 years, including representing the National Medical Association at the UN Minamata Convention negotiations. I'm also an Associate Professor at George Mason University, and I'm here to testify on the health and environmental effects of dental amalgam especially in children of color.

I'm also a member of a group called Project TENDR, which stands for Targeting

Environmental Neurodevelopmental Risk. We are a group of 50 leading neurodevelopmental scientists, researchers, medical societies, and representatives of health-affected groups. Our group issued a consensus statement in 2016 listing mercury as one of six prime examples of chemicals where there's enough scientific evidence to believe that they contribute significantly to learning disabilities, ADHD, and/or autism. We called for the reduction and exposure to mercury, especially during pregnancy and early childhood when people are especially vulnerable to neurodevelopmental toxicity from low levels of mercury exposure. As part of this, we call on the FDA's Center for Devices to end the use of amalgam in pregnant women and children and phase down all use of amalgam as required by the Minamata Convention on Mercury.

As you know, dental amalgam is 50% mercury, which is persistent, it's bioaccumulative, and it's toxic. It persists in the environment indefinitely. It bioaccumulates in fish and in people, and is toxic in all of its forms, the elemental, inorganic, and organic forms. Amalgam is now the largest use of mercury in products in the United States, making up about 50% of all mercury sales. Mercury from amalgam becomes bioavailable and contributes to the systemic body burden of mercury through inhalation and other means for extended amounts of times. It bioconcentrates in the placenta and in the breast milk, exposing the fetus during critical periods of neurological development when they are most susceptible. The neurotoxic effects may not manifest for years.

On a personal note, I have been able to measure the mercury in my breath 45 years after my mercury amalgams had been placed. I call it the toxicant that keeps on giving.

Although FDA estimates that the use of amalgam is less than 40% based on an outdated American Dental Association estimate, the truth is that we really don't know how much amalgam there is. There's no organization that tracks who gets amalgam and who

does not, what percentage of Americans get amalgam dental restorations. Based on my experience, however, I believe that the use is much lower than 40% and that it's concentrated in low-income people, the disabled, and people of color.

As you heard yesterday, we now know that metallic mercury from amalgam is biotransformed in the human body into inorganic mercury and into organic methylmercury by organisms in the mouth and in the GI tract. A 2016 analysis of 14,000 people in the NHANES database by Yen, et cetera at the University of Georgia compares people with zero, one to eight, and greater than eight dental fillings, and finds a statistically significant increase in the total inorganic as well as organic mercury levels when controlling for fish consumption and other variables. This is despite the fact that the NHANES combines both mercury-containing and non-mercury-containing dental fillings in their survey and does not distinguish between them. The authors state that the association would be even stronger if they were able to determine the association between blood mercury levels and the number of mercury-containing amalgam fillings only, but this data doesn't exist.

The same study looks at blood levels of BPA, bisphenol A, the toxicant that is in some composite dental fillings. They find no association between BPA and the number of dental fillings. This can be explained by the low level of BPA in these fillings, its low bioavailability, and the fact that it's not persistent or bioaccumulative. Therefore, there's more evidence that composites are safer alternatives to amalgam dental restoration.

The National Medical Association policy calls for the phase-out of dental amalgam in the U.S. We believe that when we have a known toxicant that is continually released and bioaccumulates in the body to add to all of the other sources of mercury, and when we have a safer alternative that's widely used because it's preferable and affordable, then we must protect those who are most vulnerable to the health harms of mercury, especially low-income children and children of color.

We call on FDA to immediately phase out the use of amalgam in pregnant women and children and to advise against public funding of amalgam for any use, as these programs serve the most vulnerable of our patients. Thank you for this opportunity to speak.

MS. TROUSDALE: Good morning. I am Kristie Trousdale, Deputy Director of the Children's Environmental Health Network, a national nonprofit that for nearly 30 years has been leading efforts to protect children from environmental health hazards and promote a healthy environment. One of the hazards we work to address is mercury. Dental amalgams are composed of 50% mercury, a heavy metal that is persistent and bioaccumulative, with proven toxicity to human health and development. An amalgam filling releases mercury vapor throughout its lifecycle, which may be inhaled and quickly absorbed into the bloodstream and carried to organs throughout the body. Biomonitoring studies indicate that people with amalgams have higher levels of mercury in their bodies than those without. An emerging science indicates that mercury from dental amalgams may be transformed in the body to methylmercury, a form that has serious neurotoxic effects.

Children can be exposed to mercury through their own amalgam fillings and can also be exposed prenatally from maternal fillings, as mercury can cross through the placenta to the unborn child, and mercury can also pass from a mother's body through her breast milk to her nursing child.

In addition, dental amalgam pollutes the environment's air, water, and soil through an estimated 28.5 metric tons of dental mercury released from cremation, sewage treatment, and other pathways. This mercury eventually ends up in our food chain, which further contributes to the aggregate exposures and resultant body burdens of pregnant women and children.

Fetal development and early childhood development are the most vulnerable periods. Critical organ systems are still developing and detoxification mechanisms are physiologically immature. Exposure during these critical windows of development can result in severe lifelong effects on the nervous, digestive and immune systems and on lungs and kidneys, and can result in brain damage, reduced IQ, learning disabilities, and hearing and vision problems, among others. The FDA itself admits that there is no evidence that amalgam is safe for developing fetuses.

In addition, each is unique, and we must consider individual genetic susceptibilities and individual mercury body burden levels from additional sources, including diet or residential proximity to polluting industry or hazardous waste sites. We must also consider individual body burden levels of other harmful toxicants and other risk factors that may lead to synergistic effects, including increased risk of harm or increased severity of harm. And we need to remember that some children have preexisting neurological problems or other conditions, and some may have allergies or hypersensitivities to mercury.

Children and families from lower-income communities and communities of color are especially vulnerable to the harms from dental mercury use. Some may have increased environmental pollution. Some may have exposures from subsistence fishing diets. Those with poor nutrition may have more cavities and, thus, more amalgam fillings, and some have additional vulnerabilities or risk factors, which could multiply the effects of mercury exposure. And often, the most vulnerable are given no or inadequate information about the risks associated with amalgams, no choice of alternatives, or no insurance coverage for alternatives.

Mercury amalgams pose unnecessary and very preventable risks to our children's health and development. The Children's Environmental Health Network strongly

encourages FDA to ban dental amalgam placement in all children, pregnant women, and breast-feeding mothers. FDA should also provide all consumers with full information about the health risks associated with amalgams as well as require dentists to provide this information during consult, and dentists should be required to offer consumers the choice of mercury-free fillings.

Finally, we encourage FDA to work toward ending all placement of new dental amalgam in the U.S. Lastly, I want to add that both the Learning Disabilities Association of America and the Alliance of Nurses for Healthy Environments regret not being able to attend this meeting, but both organizations endorse my comments today, and all three of our organizations want to thank you for this opportunity to provide comment.

DR. WARREN: Good morning. I'm pleased and honored to speak before this FDA Panel. My name is Rueben Warren, and I am a public health dentist.

Between 1980 to 1983, I was the Dental Director for the State of Mississippi. I was the Dean of the School of Dentistry at Meharry Medical College from 1983 to 1988. I'm currently Dean Emeritus. From 1988 to 1997, I was the Associate Director for Minority Health at the Centers for Disease Control and Prevention in Atlanta, Georgia. From 1997 to 2009, I was the Associate Director for Environmental Justice at the Agency for Toxic Substances and Disease Registry at CDC. And I'm currently Professor of Bioethics and the Director of the National Center for Bioethics in Research and Healthcare at Tuskegee University.

My concerns are scientific and ethical. The neurotoxicity of mercury, the absorption into the body of mercury from amalgam, the conversion of mercury from amalgam into methylmercury compounded by the preexisting disproportionate rates of neurodevelopment disorders in children of color, and the probable disproportionate use of amalgam in African American and Hispanic children poses a public health challenge and a

public health ethics dilemma.

The 2000 U.S. Surgeon General's Report on Oral Health documents that black and Hispanic children disproportionately suffer from dental cavities. Therefore, they disproportionately use and receive amalgam fillings. It is unethical to use dental amalgam in pregnant women and children until it is scientifically demonstrated that the short and long-term efficacy and safety is documented. As noted in the National Academy of Medicine text on "Toward Environmental Justice," the precautionary principle is when in doubt, err on the side of the public health. While I recognize that there is some concern about the precautionary principle and some would rather use risk reduction, it is important from an ethics perspective to consider the precautionary principle.

There is a public health ethics perspective that I'd like to share. Public health strives to improve the quality, functioning, and longevity of populations. Because public health is viewed by some very broadly, public health ethics assumes and equally broad conceptual base. Public health ethics places an emphasis on the ethical problematic related to the interest and health of groups, the social justice of the distribution of social resources, and the positive or social rights of individuals. The study of public health ethics requires that the practitioner effectively conceptualizes and operates between the tension between the individual rights and collective interests. As with public health, it also seeks to resolve an ethical problematic most effectively.

Mercury in amalgam is an ethical problem particularly as it relates to low-income children of color. I hope you will consider Medicaid guidelines, which will deeply improve the oral health of children. Thank you.

MS. LEWIS: Good morning. My name is Sharon Lewis, and I'm the Director of the Connecticut Coalition for Environmental Justice. Since our founding in 1998, we have been committed to eradicating environmental injustices by bringing awareness to the issues and

by holding governments, corporations, and individuals accountable for the crimes they commit against low-income and communities of color as they produce the unhealthy environments where people live, work, and play. There are numerous environmental injustices that I could talk about today, but I will only focus my testimony on mercury for the purposes of this convening.

I'd like to talk to you about the environmental justice communities that are segments of society that are not well known to people. Environmental justice, or EJ, communities, as they are commonly referred to, are composed of people who are living at the fence lines and/or in very close proximity to polluting facilities that contaminate their air, water, and land.

These EJ communities are primarily people of color, but almost always poor. Some of you know them as they are described today, as "marginalized" and "disenfranchised." You use terms like "disproportionately impacted," "adversely impacted." Those terms sound really good, and in fact, those terms don't even make you feel bad about it. But the reality, if you would just define those terms that I just used, you will realize that those terms don't sound so good, because we use them because we don't want to hear black, yellow, brown, or poor, because we benefit from what makes these people sick and penniless. And what they go through doesn't affect us yet. They don't affect us to the degree that it affects them. So, for now, we're happy just not facing the reality of what they go through.

But today I'd like to just describe some of the things. For example, we use, as I said, "marginalized," "disenfranchised," "disproportionate." But if you look at the definitions of these words, you will find words like "invisible," "ignored," "paralyzed," "incarcerated," "overwhelmed," "denied," "unequally burdened, "higher rates than others," These people don't have access to fresh air, clean water, and uncontaminated land. They don't have

access to full-service grocery stores and adequate healthcare. They live in substandard housing and are exposed to mercury in their water, their air, their consumer products, and in their mouths.

They don't have a seat at the decision-making tables where the rules, policies, and laws are formulated that affect their lives and well-being. And please forgive me for being emotional, but I see these people every single day. I see how sick people are because they're exposed to so many different toxins and metals. And they're exposed to the cumulative effect of all these things that make them sick and unable to work, and unable to provide for their families and to thrive.

They can't breathe, and they're regulated to life sentences of numerous chronic diseases. They are powerless because they don't have the power, political power, to stop what's happening to them. And in true Harriet Beecher Stowe form, we like to shine a light upon these injustices by making these people real, by making you understand that these people want the same things that everybody else does. We want to raise our families. We want to live in decent housing. We want to drink clean water. We want to breathe fresh air. But they are overwhelmed and overburdened, and unequally exposed, and most of all, assaulted on a daily basis by what they breathe, drink, and ingest.

So please forgive me if I don't use the words "disproportionate" or "disenfranchised," because they don't sound like what's really happening to people, and they don't describe the true nature of what's going on in environmental justice communities. These communities are already overwhelmed and overburdened with higher levels of mercury than anyone else simply due to the fact of where they live, work, and play. They live among regional industries that are sited where they live, regional landfills, regional incinerators, regional sewage sludge plants, regional nuclear power plants, highways that cut through only their neighborhoods. We don't have to deal with

all these regional facilities. They live among crematoria and superfund sites, which are basically, the cemeteries where all the amalgam that is interred in the mouths of the dead are buried.

Culturally, very few people even considered the fact that their diets are high in fish consumption, and not only do they eat fish from mercury-contaminated waters, they also rely upon canned fish, which is less expensive, tuna fish, mackerel, salmon. And has anyone ever talked about the well-known fact that high sugar consumption is prevalent in these communities? Higher sugar, more cavities, more fillings, more amalgam, more mercury, more poison in their mouths than anyone else. And think about the resulting facts of what happens. Dementia, depression, cognitive issues, renal failure, diabetes, low birth weight pregnancies, ADHD, autism, reduced IQ, brain damage, neurological issues, endocrine disruptions, nervous system issues. All can be associated with mercury exposure.

And what makes matters worse is many of the people who are exposed to mercury especially in their mouths aren't even aware that silver is really mercury. They have no idea what's happening. They have no idea that there's poison that's being put into their mouths via the fillings. Many of these people depend upon state and federal insurance programs, such as Medicaid, for their dental services, but Medicaid limits access to modern dental care.

And just when you think it couldn't get any worse, Jim Crow, the nation's system of legal segregation, has raised its ugly head again from the grave that was dug for them by the civil rights movement and was cited in a small southern New England state called Connecticut. In 2015 Connecticut's Department of Social Services issued a provider bulletin regarding dental regulations and amalgam restorations to dentists. And this provider bulletin says, "Medicaid will not pay for mercury-free restorations in the molar

teeth regardless of whether the practice markets itself as amalgam-free." It then tells dentists, "If your office cannot provide amalgam services, please have your patients call the Connecticut Dental Health Partnership so that we can locate a new dentist for them." In other words, if your dentist refuses to put amalgam fillings in your mouth, then your dentist will no longer do business with the State of Connecticut and you must find yourself one who will.

As a result, Connecticut's Medicaid recipients are segregated, separated from the typical system of dentistry that everyone else has a right to enjoy. This separate but unequal system is nothing but Jim Crow. It's amazing. And I wonder how many other states have the same policies. If you're poor, you must have amalgam, and if you're not poor, composites fine for you.

I ask you to reconsider the position on the toxicity of mercury and follow the example of lead. After many years, we're now realizing that there is no safe level of lead. How many lives are you going to sacrifice before you realize that there is no safe level of mercury exposure to humans? If it's so harmless, then why is it that when the mercury fillings are removed, it looks like a hazardous waste site, where the dentist has to protect herself, where the patient has to protect herself, where there's a mouth dam put into your mouth, where there is a respirator on your mouth? I just wonder how can you possibly think something like this is so safe when removing it is so dangerous?

History has shown itself that when white and higher-income lives are threatened, things change post-haste. I beg you to please take that thinking and get it out of your minds and your hearts and consider all lives to matter. Thank you.

MR. BROWN: Good morning. I'm Charles G. Brown. I'm President of the World Alliance for Mercury-Free Dentistry, and I work around the world to end the use of this primitive, pre-Civil War pollutant, mercury fillings, and that's how we will address this

material, as mercury fillings today. And as of July 1, 2018, the European Union no longer allows, with the most minute exception that people don't even observe because they obey it, no more mercury fillings in Europe, 28 countries in Europe, for children under 15, for pregnant women, and for breastfeeding women. No mercury fillings at all, all the way across Europe. That's considered often the kind of rival or the measurement device, the European Union and the United States FDA.

So what does the Center for Devices say about amalgam for children in their rule? They say they don't know. They don't know if amalgam is safe for children under six. They don't know if amalgam is safe for pregnant women. That's what their rule says. Well, one would think they'd do their duty and say ban it for children under six, ban it for pregnant women. Since they don't know if it's safe, they won't step up. They won't step up. The Center for Devices has a much more tolerant acceptance of mercury than the other centers of FDA. It stands alone in its tolerance of mercury and in its continual studies to try to find some way to keep going a material whose time has passed in technology, usage, and choice of the middle class, of everybody around us.

In 2006 a panel convened of you all, like Dr. Burton, and maybe some others that are here, and FDA had a question to ask: Is amalgam generally safe? They had already issued their white paper, Mr. Adjodha mentioned, saying amalgam filling, mercury fillings, are safe. The panel voted no, no, the FDA is wrong to say amalgam is generally safe. They voted 13 to 9. So FDA Center for Devices remade that vote in their literature as saying they asked us to do more studies. No. They rejected FDA's position. The Associate Commissioner for Science was so shook up when he spoke, he said, "We will change our policy." The head of the Center for Dental Devices was sobbing, having lost, and they just ignored it.

So they reconvened the panel after 2010, and the reason FDA classified it is

because they were sued, and the Federal judge ordered the Center to classify amalgam. They hadn't done it for 30 years. In 2010, when they convened again, they didn't have a vote under the ground rules, so the Center wouldn't lose another vote, but every single person who spoke on that panel in 2010, the predecessor to this one, said amalgam should not be used for children. Everyone who opined about children said it shouldn't be used. But you didn't learn that from the Center today. But they did. Again, nothing happened. In fact, nothing has happened for 9 years. Now we're back.

Now, when the presenters from the Center came, the most disappointing statement was a summary of the study which shows that pregnant women with 13 fillings are more likely to lose their babies. Statistically, there is a difference, a major difference between lots of mercury fillings and not having lots of mercury fillings. That study was explained. And then the speaker said, but it could be explained by lesser education, which is astounding and unethical. The idea -- I mean, are they saying women with less education are less interested in keeping their babies? Regardless, you have that study.

So, instead, the Center gave all this time to a study of 12 dentists that apparently showed that maybe it's the mercury -- it's the fish and not the mercury fillings, but come on. I mean, you've got that right in front of you, and the question is whether you're going to stand up.

Now, we have the myths of why we need mercury fillings, lots of myths, and all of them are wrong. Prisons. We've got to have mercury fillings, prisoners' teeth, or rather, the Bureau of Prisons uses it. No. The State of Maine Bureau of Prisons does not use amalgam, not one bit, not in any prisoner.

Well, get got to use it in the Army, very institutionalized. No. The army of Bangladesh, the army of Bangladesh armed forces do not use mercury fillings. They had a 2-year phase-out. Every new dentist couldn't use it. They gave 2 years to the others to

get training. It's not used on any soldier either. The Pentagon claims it doesn't have the money. Isn't that hilarious? Bangladesh does it. Also, a small army. Okay. Indian army, the Indian army doesn't use mercury fillings, not one bit.

Well, then they say, well, we need it for disabled children. Well, no. Mauritius ended amalgam for children in 2014. Zambia hasn't used amalgam in children, the dentists, since 2005. That's a very poor country.

Well, we need it at hospitals, they say, big in hospitals. No. The Cameroon Baptist Convention in all its hospitals hasn't used amalgam since 2007. The Vietnam has major dental hospitals in Hanoi and Ho Chi Minh City. I've been there. Big sign when you enter: "No Amalgam. Amalgam-Free Dental Hospital." I helped place the sign. It was great to be there.

Bit employers have to use it. Parker-Hannifin in Cleveland doesn't use it ever. They pay 100% for composite or ionomers. They pay 0% for mercury fillings.

Oh, public programs need them. Not in Indonesia. For three years, Indonesia does not give one nickel, one whatever they're called, riad [sic], to any dentist who uses amalgam. They pay for composite. They pay for ionomers.

Oh, amalgam -- the others take longer. No. They don't take longer once the dentist gets trained. Sweden was afraid of that, because they've converted. Everybody gets dental care. They converted to mercury-free dentistry. The dentists operated just as fast. Took a little transition. They can do it.

Oh, here's the clincher. It lasts longer. No, it doesn't. The dentists who say it lasts longer, it's no longer true. Why? The technology has changed. The technology of composite is so much better. Every dentist will tell you that. The technology of ionomers is so much better. The technology of amalgam is what it was in 1865, okay? There's no research. No one wants to research it. They shouldn't.

Amalgam is tooth-unfriendly. So, number one, it doesn't last longer. Number two, for children, it doesn't matter. It doesn't matter if it lasts longer. The tooth will be gone. Also, amalgam is tooth-unfriendly. You require removal of good tooth matter. It's more likely to crack. That's why the American Dental Association likes amalgam. It's the gift that keeps on giving if you get my drift.

The World Health Organization says it's time to focus on the life of the tooth, not the life of the filling, and the alternatives are what they call tooth-friendly. They are minimally invasive. They are massively similar these days. Amalgam costs less because the dentists are able to massively pollute the environment and pass on the costs, or the institutions. And it's continued simply because the bureaucracies don't want to change. The patients don't pay for it. There's no pressure.

The dentist in Des Moines and the dentist in Omaha isn't using amalgam. Your challenge is to change the institutions, the Medicaid, the payment systems, and the big institutions like the prisons, the Pentagon, and so on.

Now, the closing statement of all the presentations from the Center was this sentence: Turning new knowledge into more accurate casualty assessment. Turning new knowledge into more accurate -- here's something they didn't tell you. The FDA rule allows the dentists to conceal the mercury. They don't have to disclose amalgam as mercury. Why is that important? Because the ADA created the silver fillings myth. In the Zogby poll of 2014, what is the main component of amalgam, 25% said silver. It was just what's the main component of amalgam; 25% think it's silver. No. Only 40-some-percent knew it's mercury. Half knew. Half don't know. Half don't know. Was the dentist telling them? The dentist is not telling them. 11% of them learned from their dentist, only 11%. And if you're black, you're one-third as likely to learn from your dentist, and if you make less than $50,000 a year, you're less -- white or black or Latino, you're less -- one-third as

likely to know.

The NAACP has called for changes for many years. The *Journal of the National Medical Association* wrote about this. Dr. Mitchell, Dr. Warren are co-authors of the commentary along with two others, including the president of the National Medical Association, former president, talking about the injustice. Is amalgam toxic to children of color? And what was the response to this, which convened -- this was given at the Centers for Devices, that article, a few months ago. So what is their response? Not a single black doctor is on this Panel. They didn't seek out and an African American physician to sit on this Panel or an African American Ph.D. or D.D.S. And that is telling. That is telling with what's going on in America.

Now, the push to keep amalgam is the ADA. They own patents on amalgam. The ADA is a patent holder in amalgam. The ADA has a conflict of interest statement, which says if you're for mercury-free dentistry, you cannot be an officer in the ADA, amazingly. So the voices to end amalgam can't come from within the ADA. The ADA is the lobbying force for mercury fillings. They have an ethics rule, which tells dentists don't talk about the mercury. Small wonder that very few of them know. And we think the pushback from the ADA might be the reason for the inertia coming from the Center. We, of course, don't know. Boy, it's a contrast. I've sat down with the presidents of the Dental Associations of Nigeria, Tanzania, Zambia, Bangladesh, Vietnam, Indonesia, and many more. They want to end amalgam, but then, those dental associations don't own patents on amalgam.

Amalgam is as the NAACP witness said before Congress a few years ago. Amalgam is choice -- excuse me -- dentistry is choice for the rich, mercury for the poor. Now, put that in the context of body burden. Two issues, body burden on mercury, two factors: fish and mercury fillings. Okay. So we're escaping. Everybody here is escaping mercury fillings, because, hey, we don't get it anymore. So we just shifted the body burden down

to the lower socioeconomic levels. And we've conceded pregnant women are more likely to lose their babies. And we've conceded FDA does not know, the Center does not know if amalgam is safe for children. So all of these steps call for action. The Center is not going to move on that. There's just too much inertia. You need to move. You physicians and dentists, and others, need to move.

I want to finish real quick with a Civil War story, because I think it's relevant. You know how physicians used to treat syphilis. We know that. You know, drink the bottle of mercury. Lincoln's Surgeon General was so upset about mercury use, he banned mercury from the Surgeon's kit. The Medical Association was so upset. The Cincinnati Medical Association called for him to be fired. That movement spread, the pressure grew, and within a year, Lincoln had to let him go, and they returned mercury to the surgeon's kit.

Of course, fortunately, through the 19th Century, led by physicians like Oliver Wendell Holmes, the Medical Association abandoned it. They were using it in this century on the gums and on the mercurochrome, and they ended that. They said, okay, we've got to stop, stop, stop. And medicine has realized this isn't in use. Well, the dentistry, organized dentistry needs the same push that medicine needed 150 years ago. Mercury fillings is off, needs to get off the table, and you need to speak in one voice.

I'm off to the Minamata Convention on Mercury next week. I'd love to be able to say that a panel in the United States is calling for strict action as is going on around the world. Thank you.

(Applause.)

MS. HOWARD: Good morning. My name is Karen Howard, and I'm the CEO of the Organic and Natural Health Association. We're a unique trade organization in the dietary supplement space because our issues are all regarding around consumer interests. Our tenets are rooted in consumers' demands for transparency, traceability, continued quality

improvement, and accessibility to the highest-quality products available. This drives our members voluntarily strive for innovation and environmental responsibility that serves the health of the planet and the health of people. We are concerned about toxins, including mercury. The regulations governing dietary supplements, which are regulated as food, treat heavy metals as illegal adulterants, and testing is mandatory to ensure the integrity of the products.

CFSAN articulates its concerns relating to mercury in the food supply very well, asserting that low levels of heavy metals contained from multiple food sources can combine to result in higher levels of great concern. They acknowledge the need to pay attention to the vulnerable populations you've heard about today, including those with chronic health conditions, and they are particularly concerned about the adverse impact on neurological development in children, also associated with mercury.

According to a recent study, mercury contaminated almost 50% of the tested samples of commercial high-fructose corn syrup used in the processed foods our children are so happily consuming. And FDA's own dietary guidelines caution women who are pregnant or breastfeeding to source the recommended amount of seafood essential for a healthy nutrient profile from choices that are low in mercury.

Despite these concerns, and as acknowledged by evidence of FDA's new scientific review of amalgam, mercury is not stable. Elemental mercury like that in amalgam can convert to methylmercury, too. This issue is not contained to food. The effect of amalgam waste in the environment is well documented by EPA. Dental offices are the number one source of mercury at sewage treatment facilities, and the remaining sludge is deposed to landfills where it just dissipates into air and water; through incineration, where it's emitted into air or water; used in agricultural processing as fertilizer, where it evaporates into air and water. If it's medical waste, it's incinerated, again, deposited into air and

water.

We know we have a problem with heavy metal, with mercury contamination. It is no longer acceptable to assume small or even trace amounts of mercury is tolerable when it comes to the health of our most precious population, our children, especially when there are other harmless options for amalgams. The canary in this coalmine died years ago.

We urge the Advisory Panel to find mercury amalgams unsafe for this vulnerable population. We urge FDA to take action to protect our children and our future from this completely unnecessary exposure to mercury.

MS. DOVE: I'm Sylvia Dove with Consumers for Dental Choice. In its 2019 review of amalgam, FDA raises concerns about vulnerable populations, but does not draw reasonable conclusions from the evidence. To take just one example, FDA concludes that "The mercury concentrations attributed to dental amalgam in most of the reviewed studies were not sufficient for challenging overall safety of breastfeeding in the general population if devoid of excessive fish/seafood consumption or unconventional sources of mercury exposure, such as folk medicines or ritualistic remedies."

This conclusion raises three major concerns. First concern: FDA is only considering the mercury these studies attributed to dental amalgam, but many studies have traditionally failed to attribute methylmercury to amalgam. So it appears that they are likely to be underestimating this source. Furthermore, most studies are not all studies, and FDA already has enough studies to take steps to protect breastfeeding mothers and their nursing infants from this mercury product.

Second concern: FDA's review says amalgam use and breastfeeding mothers is only safe if devoid of excessive fish and seafood consumption or unconventional sources. But many women, especially in communities of color and lower-income communities are

already exposed to a lot of mercury from sources, including their environment where they encounter mercury from incinerators, crematoria in their neighborhoods, their workplaces, where the many female dental assistants and hygienists of child-bearing age experience elevated mercury levels, their cosmetics, including mercury skin whiteners that FDA acknowledges can "cause mercury poisoning or elevated levels of mercury in their bodies," their diets, for which FDA recommends breastfeeding mothers eat fish, and many eat more than recommended, whether for health, cultural or economic reasons.

If amalgam can only be used safely in breastfeeding mothers under the condition that they do not have many other mercury exposures, then it cannot be used safely in many breastfeeding mothers.

DR. RAO: Just a friendly warning. The group has 2 minutes left. Thank you.

MS. DOVE: Great. Thank you.

Third concern: Only patients and not dentists know whether they are already exposed to mercury from these other sources. But polling shows that patients do not know about amalgam's mercury content. So absent patient labeling or patient warnings, neither patients nor their dentists are in a position to discuss, much less assess, whether mercury from amalgam is too much to add to their body's preexisting mercury burden.

Among other changes, we asked FDA to revise its 2019 review to reflect that amalgam is not safe for all breastfeeding infants, especially with no patient warnings that would allow breastfeeding mothers to take steps to mitigate their mercury exposure. Thank you.

MR. DUMOFF: Good morning. My name is Alan Dumoff. I'm an attorney. I've been representing physicians and healthcare practitioners and dentists before occupational boards for over 30 years. Fortunately, the point I want to make is very brief. What you may not realize is that the statements that you make have drastic impacts on the way that

dentists are allowed to practice. So the regulations that are put in place in many states restrict dentists' ability to be able to communicate with their clients and be able to make clinical assessments about the impact of mercury and the use of mercury.

So I've litigated cases in Virginia and D.C. and worked in Maryland. And one of the central tenets of professional occupational boards has been informed consent, that when you're using emerging therapies like the stem cell, for example, therapy, you give informed consent to the patient. But if a doctor, a dentist in Virginia provides informed consent to a patient that mercury could be toxic and then replaces that restoration, they could get in trouble with the board, and they have.

There's a matter I've actually litigated in front of the D.C. Court of Appeals because the D.C. board disciplined a dentist for replacing amalgams, and the D.C. Court of Appeals found they weren't even correctly interpreting their own regulations, which actually allowed the dentist to do it. So what happens is that the dental boards think of the ADA. They think of the FDA. And they hear your concerns, and because of it, they make it difficult and impossible for dentists to properly examine, made valid clinical judgments about their patients. It interferes with their practice. And we ask you to stand down from that and to change the perspective about mercury so that patients can get reasonable care. Thank you.

DR. RAO: Thank you very much, Mr. Dumoff. I think we're going to move on to the next individual who requested to speak, and that was someone on behalf of the Indian Treaty Council. There was one speaker, who I believe is not here. Is there someone else who was going to speak on behalf --

MR. URAM: That's correct, Chair. I have her letter here, and I will read that into the record.

"Minogizheb. It's a good morning. My name Rochelle Diver. I am a member of the

Fond du Lac Band of the Lake Superior Chippewa in the Great Lakes Region, and I am representing International Indian Treaty Council, an organization working for the rights of Native American people since 1974. American Indians and Alaskan natives are already exposed to mercury in their environments. Many traditional American Indian ways of life value fish as an integral part of their indigenous subsistence culture. Indigenous peoples from traditional fishing communities in the Great Lakes area, California, Alaska, and other areas disproportionately pay the high cost of mercury contamination that impacts their health, environment, and subsistence rights.

"On top of this exposure to mercury in their environments, dental amalgam is disproportionately used in dentistry for American Indians and Alaskan natives. Dental amalgam is disproportionately used in racial minorities and indigenous peoples. Indian Health Services continues to facilitate the disproportional use of this mercury product in American Indians by purchasing even more amalgam and amalgam equipment.

"The cumulative effect of mercury exposure from the high fish diets of many indigenous peoples and mercury exposure from disproportionate amalgam use is not addressed in FDA's 2019 review. It is crucial to acknowledge that exposure to mercury in all forms continues to be a matter of urgency for American Indian and Alaskan native tribal nations because it severely impacts our right to practice our culture freely and safely. When safe levels are determined, the cumulative impacts from multiple exposures from coal-fired power plants, dental amalgams, and from consuming fish are not considered.

"High mercury levels in our women's bodies have caused an epidemic of pre-polluted babies in Minnesota. The most serious impact are on the developing nervous system of the unborn and nursing babies, and young children, and therefore, our future generations. On behalf of the 572 federally recognized tribes here in the United States, we thank you. Signed, Rochelle Diver and the International Treaty Council."

DR. RAO: Thank you very much.

The next speaker, Speaker Number 14, Carol Petersen?

MR. BROWN: Pharmacist Petersen of Wisconsin was unable to come, so I will read her statement with permission of the Chair. And I do want to say in telling the physician story a moment ago, I am the son and grandson of physicians, so I wanted so say that story very constructively for the profession.

Let me read her statement:

"Thank you for the opportunity to testify today. My name is Carol Petersen. I'm a pharmacist and hold a certificate in nutrition. I am the only pharmacist on the board of directors for a medical group which focuses on resolving metal toxicities. I am a member of the Medical Advisory Board for the Center for Menstrual Cycle and Ovulation Research. For over 25 years, I have been involved in learning, researching, coaching, and writing about endocrine disorders as my primary focus, endocrine disorders.

"We, the society, have been conducting a massive human experiment for over 150 years by placing mercury amalgam in the mouth. We have evidence that mercury fillings do leach. We have further evidence that the elemental mercury can be converted to organic mercury compounds. Mercury in the mouth can and does reach the delicate hormone signalers in the brain, the hypothalamus, and the pituitary. Disruptions of these signaling organs are devastating to the entire genesis of sex hormones, adrenal hormones, bile, and vitamin D. Damage can occur along the entire hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-adrenal axis, spilling over into other endocrine systems.

"Mercury is alone enough to produce problems in fertility in both men and women. Infertility has been skyrocketing. According to HHS, 6.1 million women of childbearing age are now unable to get pregnant or stay pregnant. Heavy metals, including mercury, are

implicated in breast cancer risk.

"But that's not all. People are experiencing chronic health issues, not only directly caused by the presence of metals in the human body, but also its interference in the delicate balance of the endocrine system. Recognition of the seriousness of these issues has even sparked the creation of an interdisciplinary field now designated metalloendocrinology, creating an interface between endocrinology and inorganic chemistry to study the needs of minerals in human health and the devastation created by heavy metals.

"For lack of a better designation, we have been observing the notion 'estrogen dominance' in both men and women. Our bodies are trying to operate with an overwhelming burden of estrogen and estrogen-like activity. The sources for this tendency are myriad. Sources are myriad:

"Number 1, excessive use of exogenous estrogens in therapy. Second, disruption of the gut flora, leading to enterohepatic recirculation of endogenous hormones. Third, loss of nutrients to provide for conjugation and elimination by the liver. Fourth, deficit of hormones that intersect and balance estrogen. Fifth, exposure to insecticides and pesticides that not only have estrogenic qualities, but accumulate in the body. Sixth, presence of heavy metals like mercury, which not only disrupt the organs of origin for hormones, but can actually block receptors, making the proper response to hormone stimulation impossible.

"As human beings, and particularly in human health, we like to think in a linear fashion. We easily understand when a toxic response is immediate and deadly. We have trouble understanding implications of slow and relentless toxicity. We have even more trouble understanding that one agent may not be the sole cause of the problems we encounter. We are confounded by the consequences of many intoxicants' magnifying

effects of each other. We like to look for solutions in a magic pill before we even understand the foundation for the problem. We are further hindered by the politics of profit, which has now so riddled our science.

"Human ingenuity has and continues to solve many problems. We can pool and magnify our endeavors to tackle problems that individuals cannot solve. Government exists as a structure needed to harness the power of the collective. We are looking to government today to recognize what was thought to be a good idea 150 years ago has significant and far-reaching negative consequences. One individual acting alone cannot solve this. We have to have the courage of our collective energies to recognize a misstep, a misstep in the cause of optimal human function and health and to adjust our actions accordingly."

This has 10 footnotes.

DR. RAO: Thank you very much.

The next speaker is Jackie Hawthorne. Is she available?

MS. ASEFA: She has a video.

DR. RAO: She has a video.

UNIDENTIFIED SPEAKER: It is a videotape, sir.

DR. RAO: Thank you.

(Video plays.)

MS. HAWTHORNE: "Good morning, and thank you for allowing me to appear in this video before your Public Advisory Committee Meeting. My name is Jacquelyn Hawthorne, and for purposes of identification only, I am a Mayor Garcetti-appointed Commissioner of the Los Angeles Housing and Community Investment Department, Vice Chair of the National Women's Political Caucus South Bay, and former president of the Los Angeles African American Women PAC, and former campaign staff to Congresswoman Diane

Watson.

"I understand the general function of your committee is to provide advice and recommendations to the FDA on scientific issues and that presentations like mine may make a positive impact on said advice and recommendations. I speak today because I have a real concern about devices containing general amalgam and their negative impact in communities of color and low-income communities.

"But, first, let me express my delight that the FDA has recently published systematic review of studies on dental amalgam involving human subjects includes a Canadian study recommending that amalgam fillings be avoided for use in the primary teeth in children, as well as for pregnant women and individuals with kidney disease. Also recommended was the use of safer dental materials. What are those safer dental materials? We know they exist. Presently, there are five types of restorative materials for tooth decay. Resin composite, glass ionomer, resin ionomer, porcelain, and gold alloys, none containing mercury. I ask that you please support these Canadian recommendations in your report to the FDA.

"Now I'll address my specific concerns. First, the FDA's literature review did not include studies adequately addressing the problem of amalgam in lower-income people and people of color. But there is already enough information for the FDA to take action. Secondly, continuing amalgam use raises multiple equity issues because of lower-income people and people of color are more likely to be affected by general mercury pollution, more likely to receive amalgam, and less likely to be told that silver fillings are made with mercury. Why more likely affected? They are already likely to have high background levels of mercury due to environmental causes, such as living near waste incinerators and crematoria, or relying on subsistence fishing like the many Latinos who fish in the Los Angeles River. It is also noteworthy that the disproportionate impact of dental mercury on

children of color is a topic of concern of the National Medical Association, the medical group for African American physicians.

"Why more likely to receive amalgam? As one study explains, 'The patient's race also is associated significantly with the material used.' Why less likely to be told about amalgam's mercury? A Zogby poll found that only 6% of African Americans report that their dentist told them that amalgam contains mercury, and Americans making under $50,000 a year are three times less likely than wealthier Americans to be told by their dentists that their amalgam fillings contain mercury, thereby depriving of their right to choose a mercury-free filling. All these factors and concerns deserve to be included in your advice and recommendations to the FDA.

"It's been a long and contentious battle. As far back as 2002, the Watson Burton Bill to abolish mercury in dentistry, HR-4163, was introduced in the 107th Congress by Congresswoman Diane Watson, Democrat of California, and Congressman Dan Burton, Republican from Indiana. Since then, the FDA has been content to sit on the sidelines and watch the game. Now I'm asking you to invite the FDA to suit up and quarterback the ban on dental amalgam.

"Thank you again for allowing me to address your Committee on behalf of the African American community and lower-income communities at risk from the use of dental amalgam.

"Jackie Hawthorne, over. "

DR. RAO: Thank you.

The next speaker is also a video, I believe? Is this Mr. Newman?

DR. NEWMAN: Yes, sir.

DR. RAO: Okay. Please go ahead. You have 4½ minutes.

DR. NEWMAN: All right. Thank you. My name is Dr. Sheldon Newman. I have been

in academics for over 40 years, 45 years. I have practiced for 25 of those years. My degree is as a dentist, also with advanced training in material sciences, and I have a master's degree in material science toxicology. Currently, I have been, and for a number of years, been a consultant with private industry primarily with the development and approval of composite restorative materials, where I've done most of my research over the last 20 years.

So if we begin this, it's important to understand what dental amalgam is. It's a set of particles to be mixed with mercury. The particles are silver, tin, copper, and some zinc, may or may not have zinc. It is important to know that it is a silver-tin alloy to be mixed with mercury, and the alloy is approximately 40% mercury once it's placed in the mouth. It's imperative also to understand that this is not copper amalgam, as opposed to the development about 30 years ago of high-copper-content dental amalgams, which are silver amalgam, and the appropriate terminology should be silver or silver tin amalgam, because it means an alloy with mercury.

Copper amalgam is not used in this country. It has not been used for, as far as I know, for over 50 years, though I understand it has been used in some other countries and still may be used there. Copper amalgam was provided to the dentist as a little pellet that was heated up just as a pellet heated up in an alcohol flame and then placed in the tooth. Because it is so close to its melting temperature, it does out-gas significant amounts of mercury. That is not the alloy that we're talking about, which is silver amalgam.

What happens is there is an initial reaction where there's conversion to conditions in the mouth. Most reactions occur within minutes; 95% of the reaction occurs in 24 hours. I have shown up there the reaction of the unreactive particle, silver-tin, with mercury. Notice there is a considerable amount of unreacted particle that's left over forever in that alloy.

There are two matrix phases, gamma one and gamma two, most of which gamma two was with our high-copper-content alloys. It is important to emphasize and understand, if you'll look at that, silver mercury phase matrix one is Ag2 to Hg3. As we go on from there, many times people have looked at and tried to identify droplets on the surface of the amalgam as being a pure mercury. It is not. I have looked at these. You will note that there are little globules -- these are pictures from ADA -- little globules that are on the surface of the unreacted particle. Further analysis by EDX identifies those as silver mercury, the gamma two phase, which will eventually completely cover that surface. It is not free mercury. It is a crystalline silver mercury phase.

As we go on from there, mercury loss from dental amalgams has been calculated from grinding many years ago. If you take those numbers by -- excellent researchers, Mahler and -- Ferracane, have done these kinds of studies. If you extrapolate those in real time to a lifetime of amalgam, in 10 years, amalgams will start to just completely disappear from the mouth if they did function the way they did their test in the laboratory. A number of people have tried to identify what's going on and that -- that are not getting there. Svara and Vimi also identified mercury exposure that is transient during during amalgam placement, and when cut out, there is not long-term -- Svara's work did indicate that there was mercury vapor in the mouth from chewing. This is done with a Jerome meter, which is subject to a high contamination with mercaptans and does not work like that.

There have been pictures identified as a exposure by heat to put amalgam into hot water. They take a picture of it, and then the spectrum that water also absorbs, so that's nothing more than hot water coming off of that. I did some studies where I looked at the amount of mercury and amalgams. The ADA actually did the test on those. And you'll find that there is approximately 40% mercury after a week of exposure to these various

temperatures. Dental amalgam in the oral conditions could last forever.

If you'll look at these pictures, you'll notice that the top one is a -- picture was taken after amalgam has been in the mouth for 30 years. The bottom is for 45 years. And there are all kinds of levels that we can talk about in the office, exposure, Minamata disease.

And what I will tell you since my time is now up, that I will thank you for your attention. This comes from a mouth that is mine that's full of amalgams, and those amalgams are now 50 years old, could not exist with some of the levels of continuous exposure that was expected from some of those studies. Thank you very much -- answer questions --

DR. RAO: Thank you, Dr. Newman.

Next speaker, you have 8½ minutes.

DR. KALL: Thank you. Good morning. My name is Jack Kall. I have no financial interest or conflict. I've paid for my travel and hotel costs.

For 42 years, I have practiced general dentistry. Thirty-six years ago, when I learned that mercury escaped from amalgam fillings, I immediately stopped placing them. I serve as the Executive Chairman of the Board of Director of the International Academy of Oral Medicine and Toxicology, a nonprofit organization. This is a volunteer position. I'm here representing our over 1,000 international dentist members.

I'd like to direct the focus of inquiry to mercury vapor, which was not acknowledged yesterday as to its equal ability to cross the blood-brain barrier just as readily as methylmercury does. Yesterday it was noted that mercury vapor is the predominant form of mercury exposure from dental amalgam, as 80% of this vapor is absorbed through the lungs during inhalation. This mercury vapor off-gases continuously from the amalgam surfaces. The rate of release increases due to any temperature increase either from hot

food and beverage consumption or friction from eating, bruxism, and tooth brushing.

In a minute, I'll show a video that was part of a study published in the journal *NeuroReport* in 2001. It summarizes in a visual way the methodology and results of this study, which can help us understand the pathophysiology of mercury. The following is a quote from the paper:

"The mercury concentrations to which these neurons were exposed .1 micromolar, were of the same order of magnitude as mercury levels reported in human and animal studies after chronic exposure to mercury vapor. The actual mercury concentration present in our neuronal cultures was indeed lower than the .1 micromolar because of the dilution effect in the culture media."

This video is about 4½ minutes and uses some time-lapse photography.

(Video plays.)

SPEAKER: "How mercury causes brain neuron degeneration. Mercury has long been known to be a potent neurotoxic substance whether it is inhaled or consumed in the diet as a food contaminant. Over the past 15 years, medical research laboratories have established that dental amalgam tooth fillings are a major contributor to mercury body burden. In 1997, a team of research scientists demonstrated that mercury vapor inhalation by animals produced a molecular lesion in brain protein metabolism, which was similar to a lesion seen in 80% of Alzheimer-diseased brains.

"Recently completed experiments by scientists at the University of Calgary's faculty of medicine now reveal with direct visual evidence from brain neuron tissue cultures how mercury ions actually alter the cell membrane structure of developing neurons. To better understand mercury's effect on the brain, let us first illustrate what brain neurons look like and how they grow.

"In this animation, we see three brain neurons growing in a tissue culture, each

with a central cell body and numerous neurite processes. At the end of each neurite is a growth comb, where structural proteins are assembled to form the cell membrane. Two principal proteins involved in growth cone function are actin, which is responsible for the pulsating motion seen here, and tubulin, a major structural component of a neurite membrane. During normal cell growth, tubulin molecules link together end-to-end to form microtubules, which surround neural fibrils, another structural protein component of the neuronal axon.

"Shown here is the neurite of a live neuron isolated from snail brain tissue, displaying linear growth due to growth cone activity. It is important to note that growth cones in all animal species, ranging from snails to humans, have identical structural and behavioral characteristics and use proteins of virtually identical composition.

"In this experiment, neurons also isolated from snail brain tissue were grown in culture for several days, after which very low concentrations of mercury were added to the culture medium for 20 minutes. Over the next 30 minutes, the neurite membrane underwent rapid degeneration, leaving behind the denuded neural fibrils seen here. In contrast, other heavy metals added to this same concentration, such as aluminum, lead, cadmium, and manganese, did not produce this effect.

"To understand how mercury causes this degeneration, let us return to our illustration. As mentioned before, tubulin proteins link together during normal cell growth to form the microtubules, which support the neurite structure. When mercury ions are introduced into the culture medium, they infiltrate the cell and bind themselves to newly synthesized tubulin molecules. More specifically, the mercury ions attach themselves to the binding site reserved for guanosine triphosphate, or GTP, on the beta subunit of the affected tubulin molecules. Since bound GTP normally provides the energy which allows tubulin molecules to attach to one another, mercury ions bound to these sites prevent

tubulin proteins from linking together.

"Consequently, the neurite's microtubules begin to disassemble into free tubulin molecules, leaving the neurite stripped of its supporting structure. Ultimately, both the developing neurite and its growth cone collapse, and some denuded neural fibrils form aggregates, or tangles, as depicted here. Shown here is a neurite growth cone stained specifically for tubulin and actin before and after mercury exposure. Note that the mercury has caused disintegration of tubulin microtubule structure.

"These new findings reveal important visual evidence as to how mercury causes neurodegeneration. More importantly, this study provides the first direct evidence that low-level mercury exposure is indeed a precipitating factor that can initiate this neurodegenerative process within the brain."

DR. KALL: But alas, I have fallen into the same trap the gentleman from Consumer for Dental Choice scolded us about yesterday in continually arguing about scientific studies, their imperfections, and all the information gaps. Yesterday I heard the following phrases: "individual variability," "underlying assumptions," "conflicting results," and "somewhat imperfect." Even though, intellectually, we might all agree that a perfect study on amalgam safety will never occur, the FDA's behavior sure doesn't reflect that. They'll keep hoping to find one forever.

Over the years, we've been told that the FDA does not consider the precautionary principle nor additive or synergistic considerations, for example, when there is concurrent exposure to both lead and mercury even though it is well documented that both together are more toxic than one by itself. Let's face it. What has been occurring the last three decades is a racket: The institutional inertia for a grandfathered substance, mercury fillings; the alleged safety of which is perpetuated by a trade organization, the American Dental Association; and which is then tolerated by the government body responsible for

protecting the public, the FDA.

I've got one word for it: Reprehensible. My call to action for the FDA is to apply the precautionary principle and start now by restricting the use of amalgam in children, pregnant women, and those with kidney and neurodegenerative diseases.

In conclusion, relative to some comments made yesterday, I've been placing composites which are BPA-free for years now. Thank goodness the dental profession has very good alternative materials. Additionally, I was the dental director of a federally funded community health center serving indigent Medicaid populations for 25 years. I've figured out how to utilize rubber dam and provide high-quality adhesive dentistry without amalgam just like dentist in the countries where amalgam use has been eliminated or heavily reduced.

Thank you for your time.

DR. RAO: Thank you, Dr. Kall.

Next on my list is Mary Starrett? No?

UNIDENTIFIED SPEAKER: Yeah. She has a audio file.

DR. RAO: Please go ahead. You have -- is this --

MS. STARRETT: "I'm County Commissioner Mary Starrett, serving in my second term as a county commission in Yamhill County, Oregon. In Oregon, the Board of Three Commissioners, each separately elected, is the governing body for the county, various service districts, councils, and committees. It's responsible for county administration, management, and policy. Our county seat, McMinnville, is 50 miles southwest of Portland. If you want to go to some of the best wineries in America, I'd invite you to come and visit us here in Yamhill County.

"The FDA's dental amalgam rule states that any change away from the use of dental amalgam is likely to result in negative public health outcomes. I want to point out how the

failure to change away from amalgam has played out in negative public health consequences for our community.

"First, I've encountered the dental amalgam issue because members of my community, especially those on Medicaid, are not receiving information about amalgam's mercury content from their dentists. They don't learn this critical fact until it's too late, and the amalgam has already been used. Patients need to know that amalgam contains mercury, because they're already exposed to so many other sources of mercury, which builds up in the body. Amalgam is one source of mercury exposure. They can choose to lessen their body's mercury burden. I urge the FDA to put this information into the hands of every single dental patient.

"Secondly, when programs like Medicaid, which we call the Oregon Health Plan, and insurance companies rely on the FDA to favor amalgam, it can limit access to dental care. Surveys show that 32 to 52% of U.S. dentists no longer use amalgam at all, and that number has been increasing. But when Medicaid or a dental insurance company will not fully cover mercury-free fillings, almost always citing the FDA, it means there are fewer dentists that people can afford to go to. Here in my state, the Oregon health authority recognized this problem. Its Health Evidence Review Commission found that relying on amalgam use in Medicaid limited access to covered dental services because many dentists have stopped using this material.

"By putting information into the hands of consumers and promoting change toward use of mercury-free filings, the FDA can help patients make the healthcare choices that limit their body's mercury burden and increase access to dental care, two huge public health benefits. Without action by the FDA, I fear this information simply will not get into the hands of low-income consumers. That's been my experience as a County Commissioner.

"Philosophically, and in the role of a County Commissioner, I believe problems are usually best addressed at the local and the state level. But providing limits on the use of amalgam or at least providing clear warnings to consumers and parents, or at the very least, ordering disclosures of the mercury to one and all, is a federal responsibility. Thank you. I appreciate the time to speak with you today."

DR. RAO: Thank you.

We next have Tom Hart, and then following that, we have Megremis.

DR. MEGREMIS: I'm Spiro Megremis, and I'm going to speak first because Tom Hart had to leave, but I will read a statement from him.

So I am Dr. Spiro Megremis, the Director of Research and Standards in the Science Institute of the American Dental Association. Also of relevance to this Panel, I am the current Chair of the Corrosion Testing Working Group of ASTM Committee F04 on Medical and Surgical Materials and Devices, which was discussed yesterday by the FDA, along with the convener of the Working Group on Corrosion Test Methods of ISO Technical Committee 106 on Dentistry, and the U.S. expert to the Amalgam Working Group of the same technical committee. Also of relevance, I joined the Society for Biomaterials as a material scientist back in the mid-'90s, and since then I have served as Chair of the Dental/Craniofacial Special Interest Group for several terms as Chair of the Devices and Materials Committee.

Biomaterials is an interdisciplinary field, and my approach is centered on materials and their interactions with the surrounding environment, which I will discuss today. Amalgam is protected from its environment by the presence of a passive oxide layer that acts both as a physical and a kinetic barrier to its surroundings. This is unlike materials, such as gold and platinum. Gold works well in the body because energetically, it wants to stay gold. The basic principles of thermodynamics can be used to understand whether or

not corrosion is energetically feasible under specific electrochemical conditions. Therefore, thermodynamics can be used to define electrochemical conditions under which corrosion is impossible.

However, when thermodynamics show that corrosion is energetically possible, it cannot be used to predict the rate of corrosion. The rate is governed by electrochemical reaction kinetics, so materials like titanium alloys, which is discussed here, and amalgam work well in the body when the tenacious oxide layers that cover them provide a kinetic barrier to corrosion that controls the rate of corrosion to insignificant levels. Therefore, in vitro corrosion testing is designed to better understand the conditions under which electrochemical reaction kinetics result in accelerated corrosion rates.

So to quote the introduction of ISO 10-271 on corrosion test methods for metallic materials, "Testing of the corrosion behavior of metallic materials in dentistry is complicated by the diversity of the materials themselves, their applications, and the environment to which they're exposed. Variation occurs between devices and with the same device during the exposure time. The type of corrosion behavior or effect can also vary with exposure time. Accordingly, it is not possible to specify a single test capable of covering all situations nor is it a practical proposition to find a test for each situation. So this international standard gives detailed procedures for test methods that have been found to be of merit, as evidenced by considerable use."

So this standard contains five test methods. However, it's in the final stages of a revision process to add four more test methods, with three of them being specific to evaluating corrosion resistance of dental amalgam. It's from standard electrochemical polarization tests like these that we know that, in general, amalgams have improved corrosion resistance by almost completely eliminating the gamma two phase, as Sheldon noted, which can be susceptible to the release of tin ions into the environment.

However, this still only happens when tin oxide covering this phase breaks down, which only happens under rare and specific conditions. Therefore, from both this standard type of corrosion testing of amalgam coupled with nonstandard testing that's done, the kinetics of ion release can be well characterized. And to go full-circle back to the interdisciplinary nature of biomaterials research, this information can be used to inform immunologists and toxicologists like on this Panel when assessing health effects to general and at-risk populations.

Thank you.

DR. RAO: Thank you.

DR. MEGREMIS: So, now, sorry Dr. Tom Hart had to leave, and he asked me to read his statement.

So Tom is the Senior Director of the ADA Association Foundation's Volpe Research Center, which is here in Gaithersburg. It's a nonprofit research group working to develop new materials to improve patient care. And I'll add -- he doesn't have it here -- but they developed the first Bis-GMA composite.

So he'd like to thank the Panel. Tom's comments are focused on dental amalgam. And yesterday, the FDA overviewed a number of reports from the public health service in 1993 and 1997, from the NIH in 2004, and from the FDA in 2009 and 2010 that assessed the literature for a correlation or causal relationship between mercury and dental amalgam and a number of health outcomes. None of these found a causal link between release of mercury vapor and adverse health effects.

The FDA has recently completed a review of the scientific literature and the clinical literature on dental amalgam. This systematic review was released in September of this year. This represents the most comprehensive review of dental amalgam from 2010 to present. In the summary portion, it states, and I quote, "In summary, considering the

totality of the evidence, including the most recent comprehensive review of clinical studies published since 2010, there is not sufficient evidence of a relationship between clinically detectible adverse health outcomes and dental amalgam mercury exposure, which is consistent with previous analysis conducted by the Department of Health and Human Services and FDA."

In addition to the Immunology Devices Panel meeting here, the FDA has also convened an expert panel to advise on dental products. The FDA Dental Products Panel has been charged to review and evaluate data concerning the safety and effectiveness of marketed and investigational products for use in dentistry and to make appropriate recommendations to the Commissioner of Food and Drugs.

In the meeting announcement, the information for this Immunology Panel, the FDA states that while not considered an implant, dental amalgam is included in the discussion because of its potential for patient and user exposure to mercury compounds. Additionally, the FDA notes for this Panel states that dental amalgam will only be mentioned briefly, as a separate review has been conducted.

This refers to the work of the FDA Dental Products Panel. And based on these findings, Tom respectfully suggests three things. One, that dental amalgam is still safe based on the most recent FDA review, so there is no urgency to take action. Based on yesterday's discussion, it is evident there are challenges to accurately measure different forms of mercury, i.e., methylmercury in its ionic form, and challenges in determining the source of mercury in diet, such as from fish or other environmental sources, including power generators, as well as from dental amalgam challenges in metrology methods to measure mercury in different forms that can be used in clinical environments.

Until these challenges are met, is it unlikely that clinical studies will provide more insights reported to date. Therefore, the Panel -- he calls to research and meet these

challenges, that they consider coordinating with the FDA Dental Products Panel to leverage their additional expertise. And Tom thanks you for his time.

DR. RAO: Thank you, Dr. Megremis.

DR. MEGREMIS: Thank you.

DR. RAO: I have Karen Palmer next, followed by Brittany Seymour.

MS. PALMER: Good morning. My name is Karen Palmer. I am a certified dental assistant. This is my third FDA hearing in the last 13 years. Panel Member Michael Adjodha, I believe you were here the last two times I spoke. I am also a registered stakeholder for the Department of State. You should have received a press release from that event on the table this morning as you arrived. Thank you.

I'm compelled once again to present myself for all the nearly other 300,000 dental assistants in this country who are first to be exposed to the enormous amounts of deadly vapor during placement and removal, lacking the serious full-body protections while serving millions of trusting patients. Currently, tests show 10,000 times the level of mercury being exposed than the higher allowable safe limit. I just want to express my sincere remorse in poisoning all the thousands of patients that I treated.

I want you to see the mask that I wore for 27 years, a paper cone-style mask. Mercury vapor goes right through it. Glasses and gloves, of course. This is a mercury vapor mask. This is what I truly needed to be wearing to protect myself.

I was diagnosed with heavy metal toxicity, mercury and lead, after experiencing extremely frightening, full-body tremors that hospitalized me twice. I was on staff at one of these hospitals. Severe paresthesia, neuropathy, fatigue. The neurologist said must be MS due to sensory disturbances and that my brain was misfiring.

Finally, an environmental doctor found me to be carrying 1,275% total mercury body burden above normal baseline. I continue to suffer from toxicity by this known

neurotoxin, permanently damaged with symptoms that are hallmark to progressive neurodegenerative diseases. Most sobering is that I am at a 40% increased risk of developing Alzheimer's from the toxic assault to my brain after giving the best years of my life, 25 years a career in dentistry.

To say that I have been deeply affected by this lethal medical and dental failure with voluminous evidence of harm, ignoring and denying repeated attempts to truly inform the public is a gross understatement. A more accurate statement of my personal feeling is we are statistically acceptable collateral damage. Sad to say. Yet this issue still remains mired in longstanding controversy and political decisions that violate the medical/dental duty of care to first do no harm.

The ADA, a trade organization that held two patents on dental amalgam, and FDA steadfastly refuse to test for safety because they know it would never pass. It would fail. This is so far beyond shameful, an organized crime against humanity, and needs to end immediately. Ban this material. It's not needed. There are no studies of safety. Just a long history of use. That doesn't make it okay.

Fact: Mercury amalgam fillings emit vapor 24/7 for the entire life in the mouth. Years and decades. So constant inhalation, breathing the vapor, swallowing, with increased levels during brushing, chewing, hot or cold food and drinks. My colleagues, dental hygienists, 300,000 of them, what about them? Beware when they're scaling, brushing, and polishing teeth. Suffice to say mercury travels the entire body, the brain, the scariest part for me until last December. Last December, I was diagnosed with breast cancer. My tumor, estrogen-positive. We know mercury is an estrogen disrupter. I am outraged with these cancer rates. Think about all this, this environmental factor.

I welcome your questions.

DR. RAO: Thank you very much.

Ms. Seymour, you have 4½ minutes.

DR. SEYMOUR: Good morning. Thank you for your time. My name is Dr. Brittany Seymour. The ADA supported my travel. I am not being paid to be here, and this statement is my own.

I'm a dentist of 14 years, a public health researcher, and Director of Global Health at Harvard School of Dental Medicine. I study how misinformation online impacts health, decision, and policymaking. Patients in the public today have access to unprecedented amounts of information. And social media sites are a highly popular source of information and misinformation. Blogs and YouTube are among the most trusted sources; 100 hours of new YouTube content are uploaded every minute; 500 million tweets are posted every day; a new blog is created every half-second.

Our research has shown that as information spreads across these platforms, we see an increased risk for misrepresentation of facts and scientific evidence. Here is what we know. Compelling personal stories and emotional content spread further and faster than scientific and evidence-based content. Non-evidence-based content negatively influences policy and harms the public when decisions are made based more on citizen petitions, cherry-picked studies, or emotional testimony rather than on sound scientific data.

Dental amalgam has remained a leading restorative material for 150 years. Studies have indicated the placement and removal of amalgam leads to a temporary elevated blood plasma level of mercury, and there is no evidence this poses a health risk. Approximately 1% of patients may experience a localized allergic reaction that can be partially or completely relieved by removal of the amalgam.

When independently evaluating whether dental amalgam poses a risk to health, expert groups confirm the following:

In the 1990s, DHHS Subcommittee on Risk Management and Committee to

Coordinate Environmental Health and Related Programs, "Data was insufficient."

1996 to 2000, NIH-funded scientific literature review, "Insufficient evidence."

1997 UK's Government on Toxicity of Chemicals in Food, Consumer Products and the Environment, "No evidence."

2010 American Dental Association Council on Scientific Affairs, "No consistent evidence."

2014 World Health Organization Consensus Statement on Dental Amalgam, "The current weight of the evidence is that dental amalgam is considered to be safe."

2015 European Commission Scientific Committee on Emerging and Newly Identified Health Risks, "No evidence."

2018 Canadian Agency for Drugs and Technology, "There is no clear reason to discontinue the use of dental amalgam in Canada."

2019 FDA Systematic Scientific Literature Review, "Not sufficient evidence."

Dental cavities are the most common disease in the world. According to the World Dental Federation, no universal substitute for dental amalgam is available to treat cavities. Currently, less is known about alternative restorative options, and they are more costly than amalgam. Based on our research, any change in recommendations for dental amalgam and not grounded in valid current evidence will have harmful reaching effects, including exacerbating existing disparities in access to care.

In summary, today one of the greatest risks to our health is misinformation and misrepresentation of scientific findings. Review of existing and new evidence must be carefully communicated to avoid misuse of data and unintentional harm to the public. Particularly related to a careful, multipronged phase-down of amalgam in response to the Minamata Treaty. Cavities are the most prevalent health problem worldwide, and dental amalgam remains, according to the weight of the evidence, overall a safe, long-lasting,

affordable treatment option for the overwhelming majority of patients.

DR. RAO: Thank you very much, Dr. Seymour.

And thank you to all of our speakers. I now pronounce the Open Public Hearing closed. The Panel will now take -- all of us will now take 11-minute break and get back into this room to start sharply at 10:30. Thank you very much.

Panel members, please do not discuss the meeting topic during the break, amongst yourselves, or with any members inside or outside of the audience. Once again, we'll resume at 10:30.

(Off the record at 10:19 a.m.)

(On the record at 10:33 a.m.)

DR. RAO: If people will take their seats, we'll get started fairly soon.

Thank you. We will now reconvene the Advisory Panel meeting. Please silence your cell phones and please take your seats.

Thank you, again, to all presenters for their briefs, testimonies, and presentations. This is now a time for open discussion amongst the Panel members. Panel members are also encouraged to ask any brief questions they have for any of the presentations that we heard this morning or yesterday. We've heard a lot over the last day and a half. There's a lot of thoughts and a lot of expertise that all of you have that helps put these thoughts into perspective. If anyone has any questions for any of the presenters, then please, this is now a time to ask them. You're also welcome to ask any of the Open Public Hearing session speakers if you have any clarify questions?

Yes, Dr. Germolec?

DR. GERMOLEC: So this is not for a specific presenter and perhaps is for the clinicians on the Panel. As a non-clinician, I would like to know what, if any, pre-implant screening or risk management or stratification is conducted prior to the placement of an

implant?

DR. RAO: Let me start off with Dr. Suzuki.

Dr. Suzuki, what pre-placement screening or risk studies do you carry out typically for dental implant placements?

DR. GERMOLEC: No, I'm sorry. I'm not asking about dental implants.

DR. RAO: Okay.

DR. GERMOLEC: I'm asking about --

DR. RAO: Orthopedic and not --

DR. GERMOLEC: Yes, yes, orthopedic.

DR. RAO: As opposed to stents or brain stents?

DR. GERMOLEC: Yes.

DR. RAO: So let me start with Dr. Jacobs, and then we'll go to Dr. Giori for your response.

DR. JACOBS: As a practicing adult reconstructive orthopedic surgeon, we go through a fairly extensive process to identify risk factors for poor outcomes following surgery. And that includes certainly a detailed medical history of conditions that might place some at increased risk, metabolic syndrome, diabetes, any other medical comorbidities.

However, I think you're asking a more specific question, and that is the risks for chronic inflammatory response or some sort of potential hypersensitivity response to the implant. And for that, there is no standardized preoperative screening. Patch tests and LTT tests are available. They're not generally recommended to do preoperatively for screening. I think most of us would ask a patient about a history of any allergies to any metals. Certainly, if they have a history of an implant, we will determine what response they may have had. And I think we generally ask them for history of any allergies to

medications and other allergies as well.

So that's usually the extent of the screening. There are other clinicians that may want to add or subtract from that.

DR. RAO: Dr. Giori, before you respond to that specific question, let me get your thoughts on what your sense is on the role of metallic hip or knee replacement implants. You know, over the years, over the last 30, 40 years, we've had this transition in where the orthopedic community focuses from focusing on surgical technique and then going to implant geometry, and then going to polyethylene wear. And now the focus currently seems to be metal consequences.

So I'm just curious. Have revision rates over these last 40, 50 years been substantially different? Are we seeing a spike now with metal implants? Are we seeing a spike in complications with metal implants? And what's your overall sense of the inflammatory effect locally from the prosthesis, and how much of that may be related to the metallic debris or metallic ion release, and your sense of the systemic toxicity from either the inflammatory component or subsequent cascade, or the metallic ion release?

And, Dr. Jacobs, I'm going to ask you the same, your response to the same question after Dr. Giori.

Thank you.

DR. GIORI: Thank you for the question. So to answer the first question, I agree with Dr. Jacobs that the extent of screening for metal reactions in general is an assessment of history of allergy.

As far as the arc of development of hip and knee replacement in particular, and I guess hip replacement would be probably the most relevant to many of the concerns that have been raised here in this Panel, definitely the hip replacements have gotten better over time, with less risk of revision. In the early 2000s, there was uncertainty regarding

what the proper, or what the best bearing couple would be, and so that's when metal-on-metal hip replacement became more popular, because people were searching for a solution to polyethylene wear and osteolysis. Over that period of time, there was also development of highly cross-linked polyethylene, and there was real uncertainty about what the final winner would be on that.

It turns out now, with the years of experience that we have since that time, the clear winner is highly cross-linked polyethylene and the clear loser was metal-on-metal articulations. It has been found that metal-on-metal articulations peaked in use in the United States around 2006, with about a third or so of hip replacements done in 2006 being metal-on-metal.

And then as orthopedic surgeons became aware of the problems over time that have been expressed by the Panelists and by our visitors who also testified, the use of metal-on-metal articulations has gone down to very low levels now, with really only essentially being used in service replacement arthroplasty, and those are rare in themselves.

With the reduction of metal-on-metal articulations, where we did see a crest of revisions due to metal-on-metal articulations, I think there's been so much attention now directed towards those that over time I expect to see fewer metal-on-metal articulations in the body and, thus, fewer revisions done for those purposes.

One positive that came out of the metal-on-metal experience is that it also heightened our attention towards corrosion at the modular taper junctions of hip replacements. Those have been described in the past but were never really recognized as a problem. With our experience and heightened awareness and Dr. Jacobs's and other people's work in this area, we now recognize modular taper junctions as being an important problem. And as a response to that, orthopedic surgeons in general are now

using fewer and fewer cobalt chrome heads. And thus, many of the hip replacements, and I might even venture to guess most at this point, hip replacements, to not have any cobalt-chrome in them at all. In other words, they're using titanium alloy stems, ceramic heads, highly cross-linked polyethylene, and then some shell that does not include cobalt and chrome.

So I think in the area of hip replacement specifically, I would expect that over the course of time with the trend towards elimination of cobalt and chrome from the hip replacement, we should see fewer and fewer problems.

DR. RAO: Thank you.

Dr. Jacobs?

DR. JACOBS: Yeah. That was an excellent summary of the state of hip arthroplasty. I would add a couple of things. First of all, the results from metal-on-metal total hips are not uniform. It really is design-specific. And not all metal-on-metal, either total hips or hip resurfacings all had high failure rates. Some actually did reasonably well.

And I think it related to a number of factors, including surgical technique design clearances, geometry, etc. So it's a fairly complex, multifactorial issue. Having said that, I do agree with Nick that -- Dr. Giori that metal-on-metal total hips are virtually nonexistent. Metal-on-metal hip resurfacing is still done, but it's in a small minority of patients, and it's generally indicated for a young, active male under 50, with a diagnosis of osteoarthritis. That's the most common indication.

The other thing I would add, however, is that the awareness of the same type of local response to metal debris has been seen fairly frequently in patients with metal-on-poly total hip replacements that have cobalt alloy heads. And when I say fairly frequently, the incidence numbers or prevalence numbers are hard to come by, but they're probably in the range of 1 to 3% of primary total hips. That is comparable to periprosthetic joint

infection. So it's arguable that one of the major failure modes of contemporary metal-on polyethylene total hip replacement is, in fact, local reactions to metal debris from accelerated tribocorrosion at the head-neck junction. The orthopedic community has responded by using fewer and fewer cobalt alloy heads. And so that may obviate the problem. There may be some unintended consequences of large numbers of ceramic heads being used. We haven't identified that yet.

The other thing I would like to add regards to the knee replacement. And there, the consideration is much less the adverse local tissue reactions, but the complaints that are fairly common of chronic pain following total knees that are attributed to metal allergy. And that is a fairly vexing problem that I see quite frequently in my clinic. There is a subpopulation of patients, maybe 10 to 15 percent, that do have some degree of chronic pain after total knee replacement, and because of the high prevalence of positivity of either patch testing or LTT, they may have a positive patch or LTT test, and it's assumed by patients and sometimes their physicians that those two are correlated.

So there's a fairly high number of patients that have symptomatic total knees that are concerned with metal allergies that we really don't have a clear diagnosis. And what's fascinating about that is how rare it is in the hip to have a patient with chronic hip pain presenting concerned about metal allergy. Really quite a different type of presentation from patients with hip replacement and knee replacement even though the materials can be similar.

DR. RAO: Yes. Dr. Taylor?

DR. TAYLOR: I wanted to address the question specifically Dr. Germolec asked initially. And I agree with what Dr. Jacobs just said especially regarding patch testing. But the bottom line is the preoperative testing is all over the place. It depends on the device. There are multiple devices. So we're talking -- I mean, the -- we talk about orthopedic

implants, and so forth, because it's the oldest and probably one of the more, obviously, most frequently used. But almost every organ system has an implant and a device, and it depends. So there are specific cases, with Nuss bars, for instance, where the people that place those -- it's a static implant. And they actually recommend patch testing and insist on patch testing, will not do the procedure until they're patch tested in advance.

As it was pointed out yesterday, the Essure device, the FDA did have a suggestion that patch testing be -- that nickel allergy was a contraindication, and then I think, as I understand it, it was actually removed. And again, it depends specifically on the device. So it's mostly patients with putative allergy to metals that we see. But, again, the patients that have putative allergy to metals, it's either preop or postop.

So preop, we do more testing in the United States. In the EU, basically, the recommendation is not to do any testing, and if there are problems, such as Dr. Jacobs pointed out, then we see those patients and evaluate them, and then the real issue is they have a positive patch test or they have a positive lymphocyte transformation test, and then the interpretation -- what's the interpretation of that? If it's clearly functioning, we clearly don't recommend the device -- the joint be removed, and we usually leave it up to the surgeon. But it's important to have communication between the two. But, again, it's device-dependent, and there's so many devices now that have metal and other materials in them.

DR. RAO: Dr. Weisman?

DR. WEISMAN: I'd like to ask my distinguished orthopedic colleagues that have spoken, including you, Dr. Rao, is there sufficient movement today in the hip replacement world to get away from the alloy and to use titanium and avoid metal-on-metal so we can be reassured now that as we go forward, that we're going to see less of these issues? From your standpoint as teachers, educators and definite influencers of other orthopedic

surgeons around the country, that this movement is going to continue and be progressive? Do I have that assurance as someone who has got to weigh these issues now about the future? Do we expect the take within the orthopedic community to continue?

DR. RAO: Dr. Jacobs and then Dr. Giori?

DR. JACOBS: In terms of total hip replacement, I agree with Dr. Giori. Probably the majority of them are done that do not have cobalt. It's titanium alloy stems, titanium allow metal-backing, ultrahigh molecular weight or high cross-linked polyethylene cup, and usually a ceramic head.

There will continue to be some hip resurfacings which are metal-on-metal currently, cobalt-on-cobalt, but it's a small number. And yes, so there is that take in the orthopedic community and I anticipate that will continue.

On the knee side, however, cobalt-chrome alloy is really the most common, far and away, so those implants will likely continue to be used. But what's different there is that, for example, a cobalt-chrome alloy femoral component, it's only one part. So there's no capacity for it to have a metal-metal contact leading to advanced tribocorrosion, which is the problem, accelerated tribocorrosion, which is a problem for cobalt alloy heads on metal stems.

DR. WEISMAN: But the hypersensitivity, for example, to the alloy will still remain a problem, because most of what we're seeing are these knees that have this -- potentially have this rare but recognizable reaction. Do you expect that to continue at a very low level, this hypersensitivity reaction?

DR. JACOBS: I would be interested in Dr. Giori's take on this, too, of the symptomatic metal allergy in a total knee, many individuals in or specialty don't necessarily accept that as a likely diagnosis. And it's really difficult to sort out an individual with chronic pain after a total knee, whether or not the immune system or some

inflammatory response due to hyper-reactivity to metal has anything to do with the symptoms.

DR. WEISMAN: I'm not asking about pain following a total knee replacement. What I'm asking about is the physical signs of erythema and hypersensitivity that, you know, that constitutes such a reaction.

DR. JACOBS: That's very rare. It's extremely rare to see that in a postop total knee. Usually the presentation is chronic pain and swelling. That's what comes to me -- and then a positive allergy test, and then they want to have it revised, or they're exploring revision. But the actual -- where there's actually a skin reaction, those are really rare. I've probably seen two or three in my career. That will remain with us, likely.

DR. WEISMAN: Thank you. That's --

DR. RAO: Dr. Giori, your thoughts on the same question?

DR. GIORI: I don't have too much more to add. I think that the difference between hips and knees, as Dr. Jacobs said, is that there is a mechanism for accelerated corrosion in hip replacement because you've got mechanical-assisted crevice corrosion at the head-neck junction or other modular taper junctions. In the knee replacement, you just have one big piece of cobalt-chrome on the femur that's not actually in contact with or fretting against anything else. And so I suspect that that's why we're seeing fewer if any -- or, well, I'd imagine that there are some in very rare circumstances, but far fewer than in the hip area.

DR. RAO: Just to expand on that, I don't have the expertise that our two analysts have on joint replacements. I do spine surgery mostly. But about 20 years ago or 25 years, or maybe 30 years ago, I did some research on wear of titanium base plates in total knee replacements. And if you wear through the polyethylene, the local wear debris from a titanium base plate is very, very, very impressive. So I don't think that replacing all the

metal we use with titanium is necessarily a solution to everything because titanium has its own issues.

In the spine, for example, if we use titanium rods, occasionally, when we do have to go in and replace them, the wear and tear at the local fretting areas between the screws and the rods, the junctional areas, titanium almost in my mind produces more local wear and tear, wear debris, than does cobalt-chrome. That's just my personal insight into this.

DR. JACOBS: Raj, can I ask you a follow-up?

DR. RAO: Yes.

DR. JACOBS: So in the spine world, where a lot of stainless steel is used, which is about 14% nickel, why isn't metal allergy a clinical issue in the spine world, and why is it in the knee world, where there's less than 1% nickel in the cobalt-chrome alloy?

DR. RAO: That's a tough question to answer, Josh. We haven't really thought about it at this point, but maybe there'll be a heightened questions of allergy after panel meetings like this.

But one of the responses may be that in the spine world, all of the tissue we put is adjacent to soft tissue, muscle tissue, and more vascular tissue, whereas in joints, there's synovium in an encapsulated area where there's potential for accumulation of the wear debris unlike in the spine. So that may be a response. That may be one area for a difference in response.

Dr. Dykewicz had a question. Then Dr. -- I heard -- I saw a hand on this side. Was it you, Dr. Taylor, or no? And then after Dr. Dykewicz, we have Joe O'Brien.

DR. DYKEWICZ: So just to reiterate a viewpoint that I've heard, that in terms of both chronic pain, and as well as joint failure from metal prosthesis, type IV, delayed-type hypersensitivity is thought to play a very minimal role relative to the percentage of patients that are experiencing problems. And then the question is even in the percentage

of patients who have demonstrated type IV hypersensitivity, the causality of it, although that is certainly a concern.

But you also mentioned that in terms of screening patients for joint implants, you took an allergy history. And this is speaking to any of the orthopedic specialists. So if you get a story, a history that the patient has a history of contact dermatitis, allergic contact dermatitis, to nickel with jewelry, does that make you avoid nickel alloys or not?

DR. JACOBS: Yes. If I get a history of that, I will order a lymphocyte transformation test. That would be the only situation that I would, actually, and to help me guide material selection. And if it's an allergy to nickel, there are nickel-free options on the market for both the hip and the knee.

The challenge comes in is if the LTT or even a patch test shows allergy to multiple metals and bone cement, and some of the assays do that. And if you follow that literally, it means the patient doesn't get a joint replacement. And so that's the challenge. And the lack of validated predictive value of these tests to predict outcomes even in a patient with a history of allergy makes it questionable how useful they are. That's certainly one of the gaps we have, and we'll address that later. We definitely need better predictive testing modalities.

DR. RAO: Giori, you have a response to that?

DR. GIORI: I have really nothing to add to that.

UNIDENTIFIED SPEAKER: Can I comment on what he just said --

DR. RAO: Let me just go to Mr. O'Brien.

MR. O'BRIEN: Thank you. Joe O'Brien. I just wanted to follow up with the point made by Dr. Jacobs regarding the use of stainless steel in the spine and a response by Dr. Rao, et cetera, in fact, I wonder if we don't have more hypersensitivity and issues with spine than what's actually reported. I think there's a number of different things. There

was a study in 2005 by Akazawa in Japan that they found 66% corrosion particularly in cross-links and places like that, and in fact, that recommendation in that study was to remove instrumentation once there was total arthrodesis, once there was total fusion that was there. Now, obviously, that wasn't followed, et cetera, and I don't know the series of that.

However, we did hear from patients, and we do have patients, and clearly, of the 10,000 patients we have in our forum, there is hypersensitivity, there is melanosis, there is people who are having many of the symptoms that have been reported here in this past 2 days that I think are underreported or underdiagnosed. There clearly is a gap issue between clinicians and the doctor. Often it gets, it gets mistranslated. They may go onto the internet and see information and hear it, and go with an emotional display. They want to get their instrumentation removed, you know, remove my rods, and everything else, and there's a gap between that process of diagnosing what's actually happening.

As you've indicated, you know, I've had six spinal fusions as an adult. I've never had any screening for any metal allergy problems, or anything else. Now, I have had some issues that sound very symptomatic to that. Whether it is or no, I don't know. I don't know.

Let me ask you a question directly. Is there any regulations that prevent you from doing screening for metal allergies? And why is it not part of the regular routine? Because of lack of clinical problems?

DR. JACOBS: There are no regulations preventing us from doing it, certainly. Whether insurance companies will pay for it is another matter. And the reason it's not done more broadly is because of the lack of robust clinical validation that these tests are going to predict outcomes.

DR. RAO: Dr. Fisher?

DR. FISHER: So, Dr. O'Brien, thank you. You got us away from joints. I will plant a couple seeds, all right? One is that yesterday in the presentations we talked about a lot of other metal-containing devices that were something other than joints. So I just say, you know, be open-minded when you have your discussions.

The other thing that I want to put out there is that a lot of times what we do is when we're designing medical devices that contain metal, right, we're trying to design these things so that they fly underneath the immunological surveillance radar, right? We want these things that are not going to be reactive in the body.

Dr. Rao asked me a question yesterday, which I side-stepped, but I want to throw it out there also to plant a seed, because I'll be asking for some input on this also. In the case of the gynecological devices that contain metal, these are actually devices that are actually intended to evoke a response, right? I mean, both the Essure device and the IUDs, they work through inflammation. Both of these contain metal. Is it the plastic? Is it the metal? Do we care? But with that in mind, if you have a device that you're going to put in and you know that it's going to evoke an immune response, going back to Dori's question, would you consider screening differently for these patients? Does it matter? So I just want to plant that seed to see if that would change how you would look at those devices.

DR. RAO: Thank you, Dr. Fisher.

Let me ask Dr. Germolec and maybe Dr. Parks after that, both immunology specialists, as to what do you think about the cons of immunological testing for metals?

DR. GERMOLEC: I might actually defer to Dr. Pollard on this, but so I or some of the clinicians that potentially do patch testing and there's a risk for sensitization -- so there is, if you do patch testing, a risk for sensitization. It's small, but it is a risk. There are additional risks. So the lymphocyte transformation test is, again, as was previously mentioned, the actual predictive nature of that for post-implant failure is unknown at this

point or is not shown to be very predictive at this point. So I think those are both cons.

I do want to bring in the point that it's been pointed out by several individuals that true metal allergy is relatively small proportion of the inflammatory component that causes device failure. And so I think that we need to potentially do a better job assessing other aspects of the immune system that may contribute to joint failure rather than focusing necessarily on metal allergy.

DR. RAO: Could you expand on that a little bit, please, Dr. Germolec? When you say metal allergy, are you talking about the types I through III, an immunoglobulin-derived response or --

DR. GERMOLEC: No. I think I'm more focused on the innate aspect of the immune response and, you know, the macrophage and neutrophil response rather than a true hypersensitivity or metal allergy response.

And one of the things that I've thought about --

DR. RAO: And how would you define an allergy response to the metal?

DR. GERMOLEC: Well, to me, true metal allergy would be a type IV response, so you know, that would be how I would define it, and that you have lymphocyte reactivity or lymphocyte specificity for metal components either, you know, haptens or the metal ions themselves.

DR. RAO: Dr. Parks and then Dr. Pollard?

DR. PARKS: I would agree with Dori, and I mean, my first sense is actually that allergy testing, the con would be perhaps a false sense of safety when, in fact, that's not addressing the true underlying risk factors --

DR. RAO: Could you speak into the microphone, please?

DR. PARKS: Well, I study systemic autoimmune diseases, so these are somewhat past the allergy hypersensitivity mechanisms. They may be later sequelae. And so patch

testing may not address that. And I think that it would be much better to take a more systemic approach to the individual's history of allergies and tendency to develop allergies, and their family history of autoimmunity, and in this age of personalized medicine, supposedly, and big data, people ought to be able to advance the science a little bit better to identify some of those predictive factors.

DR. RAO: Thank you.

Dr. Pollard?

DR. POLLARD: So I think --

DR. RAO: I'm sorry to interrupt, but could you also address how would you define a metal allergy as part of your response?

DR. POLLARD: Well, I would agree with what Dori is saying, I mean, type IV. But I think the bigger issue is that if you're going to measure or at least look at T-cell reactions to a metal exposure, they're not all the same. So beryllium is different from, zinc is different from, nickel is different from mercury. They all react in different ways. And they have their own special issues in terms of trying to figure out whether there's a specific response to that metal.

And I go back to what Dori was saying, I think the, you know, the immune system basically is there to recognize something that's foreign. That's its job. And also not to recognize self, but to recognize foreign. When you stick something in the body that's not supposed to be there, you should expect that the immune response is going to make some attempt to try and get rid of that foreign object. And the first part of that is really the innate immune system sensing the presence of that either because that particular device, or whatever, is maybe corroding and releasing debris that has sensed in as some sort of danger signal, because it's either a toxic response or there's attempts to clear it because the phagocytes are trying to clear the debris, and that invokes its own stimulation of those

cell types.

And that, then, may then spread, of course, to the adaptive immune response, but I think, at least how I've read these reports and listened the last couple days, I would think that there really needs to be a much greater understanding of what's happening as an innate immune response to these components, and how you actually try and figure out that that's actually occurred, because I think that's going to be quite difficult. I don't think that's going to be a simple thing to do. It could occur very quickly; it could take a long time depending upon how these components degrade or corrode, or whatever is happening that's actually stimulating these responses. So I think, you know, I think it's going to be a very complex situation to solve. And on top of that, of course, is the fact that there's a whole bunch of these different components with different construction, different metals, different plastics, and so forth.

So I think this is a very difficult question. And what I would like to know is the -- and perhaps I could change the subject a bit. I'd like to know what the real incidences are in terms of some of these sort of responses. I mean, are they really common? It doesn't seem like they're very common. And so is that, then, really something related to the actual patient themselves as opposed to the actual device itself? And I go back to my question yesterday: Does that then reflect perhaps the severity of the inflammation or inflammatory response that was occurring prior to the placement of this device that actually damaged those joints or caused the various pathologies that require the implantation of these devices?

DR. RAO: Thank you. I'm just going to go back to the three of you again, because I think we need to understand this. At least, I need to understand it a little bit better. When you put an implant in, and I'm sorry we're restricting it to implants at this point, but when you put an implant in, there could be a potential allergic response to maybe metal

ions that are leached out of the implant. There could also be a potential response to metal wear and tear, wear debris that gets released from local wear at some junctional area. How do you distinguish between the body's response to this wear debris versus just the body's innate dislike for the metal in the body?

I'll start with you, Dr. Germolec.

DR. GERMOLEC: That's a really challenging question. You know, again, I think to look for true metal allergy, you can -- you know, we have --

DR. RAO: Where the body just doesn't like metal?

DR. GERMOLEC: Where the body just doesn't like metal and it has a specific adaptive immune response. That is one thing. And you can assess that, potentially, with a patch test or the lymphocyte transformation test. I think a nonspecific inflammatory response, which Dr. Pollard brought up and which was what I was expressing my concern for, because I've heard in the last 2 days that the innate piece or the reason -- or that true metal allergy is rare and not frequently the cause of device failure, that to assess the, you know, the ability of an individual that's predisposed to have that type of inflammatory response would be very challenging. And I don't know other than history at this point what kinds of tests we could do, actually, to assess that other than identifying maybe the SNPs that would predispose an individual to an inflammatory response or some MHC factors.

DR. RAO: So, histologically, is there a difference between the response to a patient who has a type IV response to the metal, just dislike of the metal, versus response, the histological response to wear debris? And I'm going back to you, Dr. Germolec, and I'm going to ask the same questions to other --

DR. GERMOLEC: So I'm not a pathologist, and so I think I'd rather have that question answered by somebody that's actually looked in a joint. I would think that the

difference would be, potentially, lymphocytic versus other cell infiltrates, but again, I'm going to defer that question to someone who looks at it more routinely.

DR. RAO: Thank you.

Dr. Parks?

DR. PARKS: I'm not a pathologist either, and I wanted to say that it sounds like we're still focused on really the local reaction to joint replacement, whereas I think the discussion should be expanded to include these other metals that are --

DR. RAO: We've come to that, yeah.

DR. PARKS: Okay. So if you're asking --

DR. RAO: I just want the specific immunological difference between --

DR. PARKS: The very specific -- I don't know.

DR. RAO: Okay.

DR. PARKS: But more research is needed.

DR. RAO: Thank you.

Dr. Pollard?

DR. POLLARD: So my simple explanation is that sensitivity to a metal doesn't occur without some involvement of the innate immune response system. You don't simply get cells coming and saying, oh, there's a metal I don't like. They have to be, basically, educated or identified, really, as the cell that will respond, and that happens through presentation of either middle protein complexes or what have you.

So you would certainly need either a localized T-cell infiltrate that would come. It would have been brought there by the innate immune system mediators like cytokines and chemokines that would actually draw those inflammatory cells there from either the tissue damage or whatever has been happening to produce that sort of adverse reaction. And then perhaps you might get a T-cell population coming. But more likely what happens is

that those innate immune cells are taking debris and cellular material and so forth to lymph nodes and presenting it there to T cells.

I have read that there are some what's called a topical input structures that are produced. These normally, at least in experience with autoimmune diseases, are more normally associated with a chronic inflammatory response, and so you find them in the kidney in lupus or in the joint in rheumatoid arthritis, and so forth. But you still need that innate sensing of the presence of a danger that's occurring at that particular site or material that's being released from the joint -- or from the device that's traveling through the lymphatic system or the circulation.

DR. RAO: And would you be able to distinguish those responses between just the metal ions leached out from the implant, potentially, versus wear debris that results from mechanic phenomena?

DR. POLLARD: That is a question I cannot answer, and I don't know whether there is a way to actually answer that.

DR. RAO: And just to get a little bit more sophisticated now, you know, would that response to metal debris be different from the response to, say, polyethylene debris?

DR. POLLARD: I mean, certainly, if you're looking at T cells, the same T cell wouldn't recognize those two different things. In terms of the innate immune system, if they're recognizing that as a danger signal or a damaged material, then you would get relatively the same source of cell types. Now, I guess what's being presented here, and I don't know if Dr. Hallab is still in the audience, but he's probably better suited to address these questions, actually, because he's done this work.

But this seems like a response that involves either macrophages and probably neutrophils, and that seems, from what I've heard from him, to involve different sizes of these particles, different combinations of these particles, and so I think that may be a step

towards trying to identify what types of responses are occurring. But you'd have to go in and take a biopsy or do some sort of analysis on which you could actually do imaging that would show you specific cell types. And I'm not sure whether that sort of technology exists these days. It could certainly be developed. I don't see any problem why it couldn't be, but it would just simply be recognizing different cell types by thoracic markers, and so forth, that you could detect by imaging.

DR. RAO: Thank you.

We have Dr. Taylor, Dr. Badylak.

UNIDENTIFIED SPEAKER: Sorry, Dr. Rao. I know Dr. Babensee has been biting at the bit --

DR. RAO: I know. I have her name on the list here.

UNIDENTIFIED SPEAKER: Okay. Okay.

DR. RAO: I know Dr. Taylor, Dr. Badylak, Dr. Burchiel, then Dr. Babensee, Dr. Jacobs, and Dr. Dykewicz. So let me begin with Dr. Taylor.

DR. TAYLOR: Let me comment on several things. One, what Dr. Jacobs mentioned, because I totally agree with what he's said with the evaluating the patient with the hip pain or the knee pain that comes in, but you ordered a lymphocyte transformation test, and then it was positive to a wide range of things, including bone cement, so that in that case, that would suggest that patch testing might be able to help sort that out. And patch testing with the, with the nonmetal pieces, nonmetal chemicals, such as acrylic monomer components, which we routinely do and rarely see reactions to. Benzoyl peroxide, which is part of the acrylic monomer, has been reported and fairly well documented, but it's a difficult substance to patch test because you get false -- you can get marginal irritant reactions. But there are well-documented cases of that.

The other thing is from a clinical standpoint, from a dermatological standpoint, I

really must disagree with the concept that this is only type IV. Type I has been well documented to metals, reactions. And also photosensitivity has been reported in some cases. There are especially in type I reactions with the -- occluders. There's good studies at the University of Utah that have shown that in addition to type IV, type I reactions have occurred.

So it's important to remember that low-molecular-weight allergens still can produce type I reactions, and the difficulty is testing. So one option would be an extemporaneous RAS test, which I'm not sure if anybody can make up anymore. And, number two, it's been shown with other low-molecular-weight allergens that, you know, at least in Finland, where they tied the chemicals in with human serum albumin for testing. Obviously, type IV, I think, is the most common, the type I reactions have been reported, and I think can occur.

DR. RAO: Thank you.

Dr. Jacobs, please hold your response to that just a second.

Dr. Badylak?

DR. BADYLAK: Yeah, I am a pathologist, so I might be able to shed a little light on the earlier comment. A lot of points have been brought up. I'll try to keep my comments concise. Particulate debris will definitely cause a more aggressive inflammatory response than a single-particle. So I think this is consistent with the clinical experience that if you have an intact, say it's a cobalt-chromium joint, the incidence of there being an adverse immune response is less than if you get wear debris that's flaking around and then getting everything riled up. So from that perspective, the mechanical properties and the surgical technique become very important in determining clinical outcome.

The second point, and this relates a little bit to Dr. Fisher's comment about looking for things that fly below the immune response. Everything causes an immune response.

You don't even need an implant. A surgical incision will cause an immune response. So to look for something that has no immune response is probably not the right way to think about it. I would suggest that we focus upon saying what is an acceptable immune response, and then work on identifying those patients that are going to have an unacceptable or an adverse immune response. And that gets to the types of tests that we would like to recommend to identify those patients that are at greater risk, recognizing that nothing is ever going to be perfect.

I think there's one thing that hasn't really been talked about too much but has been -- what I think one of the most transformative findings in immunology in the past 20 years has been this recognition that there are phenotypes of inflammatory cells, of neutrophils, macrophages, T cells, and they're classically given the acronyms, you know, or abbreviations of M-1 being pro-inflammatory and M-2 being anti-inflammatory. Then you have the Th1, Th2, and the same thing for neutrophils.

So the simple presence of those cells within the tissue does not necessarily mean a bad thing is happening. In fact, in normal wound healing right now, it's, you know, it's amazing we went 100 years identifying macrophages and not knowing that there was -- that even though they look alike, you have macrophages that are good macrophages; they do good things. So perhaps the patients who present with the problems are ones where there is an inability to transition from the M-1 to the M-2 macrophage type or a continued stimulus, a co-inflammatory stimulus that's there.

And so I think this relates directly to something that Dr. Jacobs was saying earlier. I think there was a hesitation to screen all patients for their responsiveness or reaction to metals because you're likely to get a lot of patients who are going to come up positive that would never have a problem. And you can't -- I don't want to put words in your mouth, Joshua, but you can't distinguish between the patients with a positive response that are

going to be just fine versus those that are going to be not so good.

Now, one thing I do believe, what would be a huge help, is if we could identify the patients who are going to get the type IV in hypersensitivity response. If you know a patient has those immunoglobulins present, there's no way you want to put a metal into that patient who's got a known -- well, you might not -- what you don't want to do is find out about it after you put the joint it. You'd like to know it ahead of time. If you could, then you could avoid that problem.

I'd like to also suggest that in the successful outcomes of anything whether it's an intrauterine implant, a coronary stent, a joint, a spinal plate, whatever the acceptable outcome is a steady state post-response to the implant. You can either encapsulate it, you can integrate it, you can get a foreign-body response. The foreign-body response is not necessarily bad. We've been living with it for decades, and matter of fact, in many cases, you want that foreign-body response, because it elicits a fibrous capsule or connective tissue that holds the implant in place.

So all inflammation is not bad. What we have to do is figure out how do you identify the patients who are at risk for the continuous inflammation or the adverse response that is going to give some of the horrific outcomes that we've seen over the past 2 days from the public presentations. And I'll stop there.

DR. RAO: Thank you.

Dr. Burchiel?

DR. BURCHIEL: Well, there's a lot of stuff flying around, ideas. And I think that we're caught, stuck in a box a little bit, you know? The way we all learned immunology 20 years ago, and we had these type I, II, III, IVs, and it was all pretty simple. It's not the same way anymore.

There's a lot of interaction between innate and adaptive, and you saw some of

these diagrams, all these different cytokines and chemokines. It's a soup, right? And so when you go in and you do this surgery, you're going to have -- you have to have wound healing. You hit a couple of the real critical words I want to talk about. What determines whether the wound heals or you have chronic inflammation, or you trigger some other kinds of adverse immunologic phenomenon? That's partly genetically defined. It's defined by many factors, many, many factors.

So I made a list of some of the things that I want to talk about later when we answer the questions the FDA posed. I don't want to go through my list now. But I do think there's a little bit confusion about metals. Metals, you know, they can -- we talk about them as type IV, and we've been talking around this idea that they bind to proteins or peptides, and then they get presented by the innate and then a T cell, DTH, Th1-type T cell will respond to it, because it has an antigen receptor that recognizes it.

And we know that those receptors, which are unique amongst all of us, we all have our unique Class I and Class II receptors. Our speaker from Chicago talked about that the other day. We know a lot about what goes on with other metals. Like beryllium, we know a lot about susceptibility to beryllium and what are the risk factors that determine whether you will be sensitized, and you'll have a positive lymphocyte test, which is what they do for beryllium, too, to predict something that'll happen maybe 20 years from now, is when you get chronic granulomatous disease with beryllium.

These metals are similar, but they're different. That's what, you know, was being said by Mike Pollard. They're similar, but different. So I think that we have types of reactions where metals tend to bind things. They bind nonspecifically to albumin, but they bind specifically to other proteins. That's the key. We don't really understand what the metal peptidome is, what metals/peptides are they, in effect, binding. People do this, but how informative is it to us as you as clinicians, in terms of using that in your daily work,

you know? That's a difficult thing to do. It's a high bar.

But I will make one other point. The metals, Dori started off -- Dr. Germolec -- excuse me -- started off by presenting the immunotoxicology balance of too much and too little. Immunosuppression would set you up for infections or cancer whereas immunostimulation maybe you're going to get an autoimmunity. Nobody really knows the answer to that really, although some of the new drugs that are being developed, you see them on TV every night, the biologicals that are being used for stimulating cancer, oh, yeah, we know they are causing some autoimmune problems. They are stimulating your natural defenses to fight cancer, but they're also stimulating your autoimmune. So this idea has probably got some merit.

There are some ideas about just stimulation, just immunostimulation. And we understand that metals, many metals, are what we call adjuvants. They nonspecifically stimulate. So this is where we get into a problem with this idea of allergy and hypersensitivity, and your genetic susceptibility versus the idea that some metals are nonspecific adjuvants, and they will just stimulate generally. They're immunostimulants.

And then the last point I'll make is that some of those metals, as again was pointed out by one of our speakers, they bind to very specific proteins not so they could be presented as an antigen, but they actually modulate the function, signaling molecules, zinc finger proteins. Some of the metals bind to those zinc finger proteins. And that interferes with their activity.

So as we say in toxicology, the dose makes the poison. Do you get enough free metal to interact with proteins in that way that will have toxicity, overt toxicity? If so, you know, we all believe we'll all respond at some dose, right? We'll all respond at some dose, but we probably never reach that dose with an implant, with a prosthesis.

The amount of free metal, unless you have something catastrophic -- I mean, I've

been learning about cobalt, and it seems like in some cases, you can get a lot of free metal, and that can be very, very toxic to your body. But I'm saying for the very low concentrations, staying-below-the-radar-type concentrations, you may be okay.

But there's more going on there than hypersensitivity. That was my big point. There's other mechanisms that are very important. Immunostimulation, immunomodulation is part of what we're talking here. And we're part of talking about risk when metals are circulating in the body, foreign metals. You don't have a lot of these metals in your proteins typically. They may stimulate in ways that we don't anticipate. And so I'm going to stop with that, and then I could give you my other points when we go through the list.

DR. RAO: Thank you.

Dr. Babensee and then Dr. Jacobs and then Dr. Dykewicz.

DR. BABENSEE: So there are several things that I would like to respond to. Hopefully, I'll remember them all.

I think the first thing is some comments on terminology that's being used. And so the innate response is a nonspecific response, and that can occur to a biomaterial, a foreign implant, with an inflammatory response. And so that would be the type of response that you would have to particulate matter, you know, with an increase in the surface area, with particulates being formed that would activate or stimulate the inflammatory macrophages, in particular, to take up those particles and try to destroy them so that it would cause the inflammatory response and be a stimulus there. And that could act as a chronic inflammatory stimulus.

And with the adaptive immune response, there needs to be an antigen. There needs to be something presented on the MHC molecule to a T cell that recognizes it and then stimulates clonal expansion of the T cells and also antibody generation. And so, you

know, my question yesterday was: What was the antigen? And so I would still like us to define what that is and what it could be, and you know, one of the comments I have for the questions that we have to answer is, you know, can we determine what is the mechanism of that allergic reaction, and what is the antigen?

So, for example, I do not see how you can have a allergy or have an adaptive immune response to a metal or a metal ion. If there's a metal ion that's bound to a protein and has somehow changed that protein's confirmation, or something like that, then you could have the immune response to that.

The other thing is using the terminology "immune response," you know, normally I think people will think of that as the adaptive immune response or an antigen being involved in the immune response. So I think we have to be careful. And, you know, if we say immune response, we may be talking about both arms of the immune response, but I think being more clear that it's the innate immune response or the adaptive immune response that we are talking about, or potentially, I use an inflammatory response for the innate immune response to a material and then adaptive immune response for where there is an antigen.

And the other question you had was about how you would distinguish the metal ion effect versus the particle generation effect. I think you would see the metal ion when you have that ion detected in the blood or when you are able to test for it and show that there is stimulation of T cells, or something like that. So I would just caution us to be careful with how we're using our words for some of these terms.

DR. RAO: Thank you.

Dr. Jacobs, you had a response to Dr. Taylor, and you also had your own thoughts.

DR. JACOBS: Yes. Thank you. So in terms of your point that perhaps patch testing could be helpful when the LTT test comes back with multiple positives, the problem is I see

patch testing results often the same; the patch tests positive to multiple metals, including patch test positivity to bone cement and their components.

One of the things that individuals -- and maybe this is true more of clinicians than some of our immunologists -- is they don't recognize the concept of bioavailability. And just because you have either patch tests or LTT-positive to a particular metal ion or metal salt doesn't mean that that -- even though it's in the alloy, that it will be in a bioavailable state to actually elicit an immune response.

So, for example, when you talk about the components of bone cement that you're testing, they're probably only in a sufficient bioavailable dose right at the time that the cement is curing, and after that time, the accelerators and suppressors of the bone cement reaction, they're probably gone. So the relevance of being sensitive on patch testing to a component of bone cement is probably not very high when you're talking about, you know, a period of time far after the cement is cured. I also want to address the issue -- so, in other words, I don't think patch testing helps sort that out.

I think, actually, when you see one of these cases -- and it goes to a point that was previously made -- where there's multiple positivities to either patch or LTT, you are actually measuring a heightened immune -- or a heightened immune surveillance response in that individual patient. Somehow their immune system is hyper-stimulated, and what that means in terms of the outcome of their joints I think we haven't worked out. But I think that is a marker for that.

In terms of the histology, I am not a pathologist, but there's a tremendous amount of literature on distinguishing, you know, a macrophage response from, potentially, a hypersensitivity response, adaptive versus innate. The whole concept of the ALVAL, that's aseptic lymphocyte-dominated vasculitis-associated lesion, was described by Hans Willert and Patrick Case and Pat Campbell when they were trying to describe what they thought

was a fairly unique histology around patients with metal-on-metal devices that were symptomatic without other obvious causes. So they thought that this could be a marker for an immunological response to metal debris.

The problem is they didn't called it a DTH response because the ALVAL is not quite the same histologically. Furthermore, you can see ALVAL responses in patients undergoing primary total hip replacement. In other words, individuals that have osteoarthritis, you can look at their histology, and there can be spots and patches of ALVAL in that tissue as well. So it's a complex thing to sort out. That's why Pat Campbell and others have -- an ALVAL scale, but even that really hasn't been what I would call pathognomonic or diagnostic of adverse local tissue reaction or an adaptive immune response.

I also want to address this concept of, potentially, a type I through III reaction potentially giving a symptomatic metal allergy case. And I would agree with Dr. Taylor. It's probably not all type IV. Anecdotally, I've seen two or three cases in my career of individuals who had high metal levels from a failed metal-on-metal device, a Coombs-positive hemolytic anemia, which is often associated with antigen antibody interactions, and then resolution of that anemia, decreased cobalt levels when the implant was revised.

There is a literature, as I mentioned before, from Kathy Merritt, about antibody production to metal debris. So that's a gap area in understanding type I through III reactions and how that may participate in what we're seeing.

And then I'd like to make two other points. One is it's very difficult to distinguish between a particulate effect and an ionic effect on the local tissues because once wear debris lands in the tissues, it produces metal ions; the wear debris corrodes. So that's a source of ongoing metal generation.

So I'd like to stop my comments my asking my colleague to my right, Dr. Germolec about the relationship between autoimmunity and some of the processes we're talking

about for metal implants, whether you call it hypersensitivity or allergic responses, or what have you. What is the bridge? Is there cause? Is there effect? I would say, anecdotally, I have seen some very bizarre reactions in patients that come in with a known diagnosis of, say, systemic sclerosis or psoriatic arthritis. Sometimes I see fairly bizarre reactions to their metal implants, rapid loosening, etc. And so what is that relationship between autoimmunity and this process we're talking about in relation to metals.

DR. RAO: While you think of your answer, Dr. Germolec, let me just ask Dr. Dykewicz and then Dr. Weisman to ask their questions.

DR. DYKEWICZ: I was going to interject something that I think may be helpful in terms of lessons learned and potential analogies with asthma and occupational asthma. For instance, in occupational asthma, there are cases of, for instance, platinum-induced asthma, that are thought to be IgE-mediated. There is the thought that we have a lot of low-molecular-weight agents that cause occupational asthma. There is a conjugation between the small-molecular-weight agent and cell proteins that serves as the overall antigen that then stimulates the immune system. So certainly back to Dr. Taylor's statement, too, about IgE sensitivity being a part of this, it could be. I think it's probably a small part.

Now, in terms of, though, innate immunity with asthma, this is something that has been recognized now as being of increasing importance. And I think this is important for our purposes today, because my takeaway is a lot of what we're dealing with is an innate immune responses. And you can't by doing adaptive immune response testing to things like LTT or delayed patch testing, you can't assess what the innate immune responses are going on.

So we know, for instance, that with asthma, you can divide into allergic versus non-allergic. You can also divide it into whether it's eosinophilic-driven or neutrophilic-driven.

Of the eosinophilic-driven asthma, it has traditionally been thought that IgE to -- allergens was causing the problem. What we now recognize, there's a subset of patients, they get eosinophilic responses, they have no IgE allergy, and the concept is that the airway innate immune system is being activated by danger signals, such as viruses, other agents. And so, again, I think it's important that we look at the innate immune system as being a driver. And that's very problematic. There could be polymorphisms in toll-like receptors that's making a difference as to why some patients have responses that are adverse and others aren't. But, again, I think innate immunity is going to be a big focus of our research needs.

DR. RAO: Thank you.

Dr. Weisman and then Dr. Lemons and Dr. Babensee and then Dr. Germolec?

DR. WEISMAN: The two big clinical problems are pain following an implant and the question about whether or not these implants trigger some systemic rheumatic disease. I mean, those are the two issues up here.

So what have we learned about what are the triggers of systemic rheumatic diseases? What have we learned in the last 10 years as our tools have sharpened? Well, pick rheumatoid arthritis, for example. That we now can identify 10 years before patients that get rheumatoid arthritis, we can identify things in the bloodstream that predict it. And that's very interesting because also -- and cigarette smoking is the major trigger for seropositive rheumatoid arthritis in the world. And as you can trace the decline in rheumatoid arthritis incidence, prevalence, and severity, actually, actually, to the decline in cigarette smoking worldwide.

So when that's done, many people have the cytokine trigger first that comes in perhaps through the inhaled antigens from cigarette smoking or pollution, but it's mostly cigarette smoking. Then you will see a peak in cytokine response. Then it goes away. And some patients never get rheumatoid arthritis at all, but if you have a certain HOA type, you

will at a much higher rate. And you can follow those patients over time, and it looks like there's more than one hit to get rheumatoid arthritis, right? Your genes are there to begin with, but there are multiple hits. So that's telling you something about the relationship between the immune responses and a chronic rheumatic disease. So I'm trying to look at an implant and see whether that has any factor in any of this.

Now, let's look at another disease, ankylosing spondylitis, for example, highly genetically determined disease. If you have the right HOA B27 antigen, and you come across a very toxic bacteria like *Salmonella* or *Shigella*, which has a huge impact on the GI tract, you know, produces horrible, explosive bloody diarrhea, and you're B27-positive, you have a very high chance of actually triggering a lifelong systemic rheumatic disease, maybe 1 in 4, 1 in 4 of those people.

All right. But what if you don't encounter that highly toxic bug, something less toxic like a *Campylobacter* or something? You may have actually a milder form of spondyloarthritis. That's number one. And number two, even if you have ankylosing spondylitis, now people are looking at the composition of your microbiome and see whether there is some kind of special relationship between that microbiome and ankylosing spondylitis. But the time course of these events, these rheumatic diseases, are decades long. And there are multiple ups and downs that occur through this.

So I'm trying to piece -- this is what we're -- what's emerging in understanding the immune basis for two really well-described phenotypes, the ankylosing spondylitis and rheumatoid arthritis, I'm trying to extrapolate that kind of information back to what happens when you put an implant in somebody. Is it do you think that the metal ion or the metal combination with a protein, or is there some adjuvant effect of debris, you know? Do we think that there's enough evidence anywhere to show that those activities can behave like the environmental and genetic triggers for diseases that we already know

about?

Okay. Is there enough evidence for that phenomena to take place in your world of metal implants, right? Well, I don't see that. I mean, as I look and read and think about these things, I don't see where these two things -- these two paths cross. And to sit around and talk about Types I through type IV, you're talking about something that occurs at one point in time. But we're talking about diseases that take years and decades to develop. Where is that in metal in the human body? I don't see it. And like, tell me, you know? Bring me, who tries to understand chronic rheumatic diseases, up to your speed and show me where your triggers are coming in and producing one of my diseases, you know, one of which is staying and one of which is going away?

DR. RAO: Thank you, Dr. Weisman.

Dr. Lemons and then Dr. Babensee and Dr. Germolec. I think we should try and conclude this part of the deliberations in about 15 minutes or so, and we'll try to address some of the questions that the FDA has for us. And then during the course of our responding to those questions, I think more of the discussion will come up, but this open discussion, I think we should try and conclude in about 15 minutes or so.

Dr. Lemons?

DR. LEMONS: I'll preface my remarks by saying that over more than 40 years, we've conducted a device retrieval and analysis program that's composed of monthly meetings during most of that period that included pathologists, the clinicians, plus physical scientists from multiple disciplines. And I think there are a number of lessons important to what we're doing here.

Simultaneously, I directed and co-directed a histology/histomorphometry core laboratory for our university and the country now. The point that I would like to make first is when we talk about this, there are many things in common between dentistry and

medicine. And 20 years ago, we spent a great deal of time and developed a whole series of books and activities in terms of allergic response to metallic materials, including polymerics, etc. And I think that literature is relevant.

The second point that I would make is when we talk about the substance and the debris, what we have found considering a total of about 7,000 evaluations, 2,000 of which were associated with devices that had not reached revision, the others had reached revision, and it was a mixture of all types of devices, is that the debris is quite variable in terms of its underlying chemistry when you do SEM/EDX, or analysis of the debris or sequence it out, or centrifuge it out. It's variable in size. It's variable in shape. It's variable in amount and variable in location. And it's very specific to the location that it exists in when you analyze it in terms of, say, the response.

If you take the simplistic approach of saying cobalt, please realize that in dentistry, there are multiple cobalt alloys that have been evaluated. But if we take the step of going to orthopedics or other disciplines, there's at least eight principal alloys that are all different than one another that produce a different debris. So the point I'm trying to make is we need to understand not only the biological reaction, but the physical science aspects or the material science of what it is that we are analyzing specific. And if we expand to titanium alloy or titanium, it's the same issue. There's a multiple series of alloys. And then if we go into stainless steel, that's fairly uniform, but there have been a variety of steels and other materials, and same as nickel titanium.

So the point I'm trying to make is this whole issue needs significant combined scientific analyses that include both the physical and biological science of what we're doing.

DR. RAO: Thank you, Dr. Lemons.

Dr. Babensee?

DR. BABENSEE: Yes. I would like to echo also what Dr. Lemons just said. And I think in thinking about this problem, you do have to think about, you know, what material aspects are -- how are they connected with the host response, and so making that connection. And that takes a multidisciplinary team or people who are trained in multidisciplinary areas. So, you know, I have training in biomaterials and polymers especially, but also in the histology and the in vivo responses.

So another thing is the thinking about the biocompatibility of materials, and the recognized definition for that is to have an appropriate host response for a particular application. So it matters what the intended application is. And so I would just recommend that we think about not only the devices that we're discussing here, but other devices that we can also see failures with or good responses to.

And the other issue is the issue of an adjuvant. And so an adjuvant is something that will stimulate the innate immune response or stimulate inflammation and be used to enhance the immune response to a particular antigen that's co-delivered at the same time. And so, again, just to make that connection, I think the word adjuvant was used previously. And so it does -- it could influence -- your initial innate immune response to the implant could have an effect, then, on the adaptive immune response to the antigen or the metal antigen combination.

And it could also -- you know, a lot of adjuvants are thought to work through toll-like receptors, but it can also be just a general stimulation of the innate immune cells like macrophages and dendritic cells so that they're better at antigen presentation.

DR. RAO: Thank you.

Dr. Germolec, if you could respond to -- could someone turn my microphone off?

DR. GERMOLEC: So I'd like to thank Dr. Weisman for actually bringing up a number of points that I would have raised in response to your question.

So I think, in general, you know, I think of autoimmunity as immune stimulation. As Dr. Burchiel pointed out, you know, immune stimulation is a response to a number of things. I think that individuals that have autoimmune disease have a propensity either because of underlying genetics or because of environmental triggers, several of which were brought up by Dr. Weisman, that they develop kind of a hyper-immune state.

We understand so little about the things that actually regulate autoimmune disease. We know that there are environmental triggers. We know that genetics are important. But we know that neither one of them individually, except for in a few very rare cases, one of which was brought by Dr. Weisman, we know that neither one individually is a specific predisposing factor.

So twins, identical twins, which, you know, this is common knowledge, identical twins with identical genetic makeup, one can get autoimmune disease, the other twin does not. So we know that there are environmental factors that trigger. We know that there are many factors in the environment, viruses, and latent viral infection is one that maybe Christine can talk about. But these are things that are nonspecific, you know, cause nonspecific stimulation of the immune response. And when you get that in the presence of other triggering factors, such as metal debris, then, you know, in combination with perhaps underlying genetics, you can develop autoimmune disease.

So I think it's very multifactorial, and I think that it's very difficult to understand what predisposes. I think each patient is different. Each patient has a different underlying genetic makeup. Each patient is exposed to a different set of environmental factors, lifestyle factors. So what we need to do is understand perhaps how the combination of those factors might contribute to autoimmune disease or systemic hypersensitivity. But I think that, again, it's a picture that is very multifactorial and would be very difficult to get a handle on.

DR. RAO: Thank you.

I'd also like to acknowledge that this was also raised during the Open Public Hearing section of the meeting, where some of our members of the audience kind of raised the whole concept of triggering of the immune response.

Someone raised a hand. Yes, Dr. McDiarmid?

DR. McDIARMID: Thanks. I would like to say something that maybe is a little less biologic, but more patient-centered and maybe somewhat responsive to some of the testimony that we heard yesterday. Related to Dr. Jacobs's comment about pre-surgery testing with lymphocyte transformation tests. And yes, it only addresses theoretically and even maybe in an unsatisfactory way who might have some type of a true metal allergy or a type IV kind of problem.

I think in addition to that, you do it as a reason, as you said, to help you select maybe devices. But I think it also informs the informed consent conversation, I would think, even as that would be a little bit still messy, because that test does not really map perfectly to, you know, why you're using it, but you're choosing to explore that. And I think one of the sources of harm that we heard yesterday was some patients felt that they were not adequately informed of potential problems. And so I would think this is, albeit messy, but if it's something you think is worthwhile, you would then be able to bring that to the informed consent conversation.

DR. RAO: Thank you. And, Dr. Parks, you had a question?

DR. PARKS: Well, I just wanted to also thank you for bringing up this issue of the natural history of the development of autoimmunity. One of the only other established environmental risk factors for systemic autoimmune diseases is crystalline silica or quartz dust in the occupational setting at very high levels. It's known to be associated with rheumatoid arthritis, lupus, systemic sclerosis, again, bringing up this idea that a

nonspecific immune adjuvant may contribute to the development of an autoimmune disease, that the phenotype may be driven by other factors, genetic or other environmental factors.

So I think that's one point to bring home when you're thinking about metals and their reactivity. I haven't heard much about what happens to metal particulates in the body, whether they become sequestered in immunologic organs and, you know, silica will do that, and it will sit in the body for decades, because it can't be destroyed. So I haven't heard that.

The other thing is we really do have a very poor understanding of the natural history of autoimmune diseases, although we do now understand that preexisting system autoimmunity may exist decades prior to development of clinical disease. We don't know what those triggers are along the way. So --

DR. RAO: Thank you.

DR. JACOBS: Yeah, I can --

DR. RAO: Just a couple of things -- go ahead, Dr. --

DR. JACOBS: I just wanted to respond to Dr. Parks. There is a literature in orthopedic devices looking at autopsy retrievals that the liver, spleen, periaortic lymph nodes are a common sink for a lot of metal debris. So it does -- and that's fairly well reported. Also been reported recently is it's commonly found in the bone marrow, particularly in individuals that have had high -- situations.

DR. RAO: We've talked about this immune response to a degree, Dr. Dykewicz. Do you have any thoughts on the role of systemic toxicity to the metal and how that might be overlapping with some of the clinical manifestations of this whole role? Is there -- what is the impact of systemic toxicity versus the immune response, and how do you -- is it possible to distinguish the two? And --

DR. DYKEWICZ: It's a very difficult and important question, which I think points out a knowledge gap. There certainly are situations where you have local exposure to some antigen, and that results in not only local immune responses and pathology, and just, for instance, bringing up an easy example of asthma, that also is associated with rhinitis because of trafficking of immune cells throughout the body. But more specific to the metal question, there are cases where people will have nickel allergy. And this is thought to result in some multisystem dysfunction. It's not well understood. That seems to be kind of rare.

But I think rather than be able to give you a conclusive answer that's evidence-based, I think more than anything, it just points out that we have the need to study more what systemic hypersensitivity responses there would be, for instance, having rashes, from metals. But then sort of I would almost kind of say in a converse way, with autoimmune disease, I mean, the immune system in some ways is thought to be skewed to hypersensitivity responses versus autoimmune responses and why some people go one way versus another. Seeing a shaking of the head. But, you know, for instance, in concept with IgE hypersensitivity disease, that is thought to have a different T-cell subset with Th2 versus Th1, which is more associated with rheumatologic autoimmune disease. However, Th1 also does get involved with type IV hypersensitivity. So it's messy, and I don't think I can give you a good answer.

DR. RAO: Dr. Burchiel, since he does a little bit of overlap between both toxicology and immunology, any thoughts? Systemic toxicity versus immunological responses long-term? Or we can do it in the --

DR. BURCHIEL: I think I'd like to do it as we go through.

DR. RAO: As we go through the questions?

DR. BURCHIEL: I've sort of laid that out in kind of a linear way.

DR. RAO: Sure.

Dr. McDiarmid, any thoughts on that specifically?

DR. McDIARMID: That's not precisely my area, so --

DR. RAO: Okay. Thank you.

UNIDENTIFIED SPEAKER: Can I comment?

DR. RAO: Dr. Lemons had a question, and then we can go to you, Dr. --

DR. LEMONS: Just wanted to add. I forgot in my last statement to make the comment a great deal of what we see at the tissue interface with implants is not metallic debris from the implant, but metallic debris from the instrumentation or association of the procedure, where a variety of substances can be used that sometimes are not cleaned out of the site adequately.

And where we experienced that was in the proposed failure of a series of dental implants made of alloy titanium, and within that series, what we found, it was actually the instrumentation for cutting the bone that left the debris in the interface, which then became a galvanic interaction between the steel residual products, high nickel.

The other issue that we found that was of significance was chronic exposure in some populations of significance. And the one that was very much an issue was piercings. And the coating of gold that was over the nickel-based alloy, where the gold acted to produce crevice corrosion in the site of piercing, and the chronic delivery of substances. So there's multiple confounding factors that can enter into our discretion.

DR. RAO: Thank you.

Dr. O'Brien, then Dr. Giori, and then let's stop at that point here.

MR. O'BRIEN: Thank you. Joe O'Brien. I just wanted to make sure I have a full understanding again of immunology responses. Is it just an issue of metal or getting back to your question again, or is it metal or some other component? And I'd like to actually

pose it in a very specific question so I can understand it.

So, for example, relative to risk, or potential risk, you know, in adolescent spinal fusion, current standard is to use a variety of pedicle screws of different metals, and then you use, let's say, stainless steel rods that are connected to those screws, and then some various other cross-links or others that may have occurred there.

There's a new technology now that is going to potentially replace those stainless steel rods, and instead use a polyethylene cord in its place. So -- and instead of fusion, it's now going to be, you know, save those segments and allow growth modulation to actually change the curve. So what you have is you remove a large surface area of stainless steel, but on the other hand, you now have constant movement that is allowed within the spine.

So is it wear/tear, or is it, you know, response to ions, et cetera? Which one is more harmful? And as we look to emerging technology, are we potentially going to create more harm from an immunological perspective or less?

DR. RAO: Thank you. Just FYI, we did review a similar type of implant many, many years ago, and the nonmetallic implants had some of their own issues.

Dr. Giori?

DR. GIORI: Yes. I'd like to at least raise a concern that I have as a practicing orthopedic surgeon. I need some help, basically, in order to be able to define what is the syndrome that we're all trying to understand.

So I think it would be helpful to, much as is done in rheumatology, to define a series of signs and symptoms or laboratory values that then can be used to define a particular syndrome. Once you have a syndrome that is defined and agreed upon, it makes it a lot easier to study it. And without having that definition, I think it becomes much more difficult. So it's a plug for that.

DR. RAO: Thank you. I have good news and bad news for you. I think that's a valid

question. The bad news is you're going to help answer that question.

(Laughter.)

DR. RAO: Let's go to the questions and just get a sense of where we stand. And I want to change the order of the questions just a little bit and maybe address Question 4 first, which has to do with the testing for these conditions.

So it says: "Please discuss the status and clinical utility of available diagnostic and prognostic tests for pre- and post-procedural assessment or management of possible implant or insert-related host reactions."

So this is the question. You know, they want us to give them some information on pre-diagnostic or prognostic tests for pre- and post-procedural assessments.

And maybe I'll start with you, Dr. Jannetto, and then I'll go around the table, and we'll respond to this.

DR. JANNETTO: Sure. So I think a key thing to realize here, and it's come up over the past several days, but it's also available in the literature, is that a lot of the testing that is performed is not standardized. And that includes the immunological testing, from the lymphocyte transformation test and the patch testing, which has come out and has said that the varying forms of salts versus oxides that are used can cause differences in response, as well as the concentrations that are used, if they're physiological or not. So it's no surprise that literature doesn't have consistency in findings using these same tests when they're not standardized.

And my area of expertise is on elemental analysis. We've heard through presentations yesterday that ICP-MS, inductively coupled plasma mass spectrometry, is the predominant method used to measure metal ions in the body. It should be noted that the concerns that were brought up around that testing also can make those results confounding or confusing in many different studies. The pre-analytical issues, I cannot

stress to you, are probably the most important finding that we find in our labs, where we see falsely elevated results.

DR. RAO: What do you mean by pre-analytical issues?

DR. JANNETTO: Pre-analytical issues like the issues that were brought up yesterday, everything from the blood draw and collection process, from the needles that were used, to the special collection tubes that are used. When we talk about measuring things like serum, even then, when you have to centrifuge the sample and aliquot off the serum, if you pipette that versus pour that off into another container, that can actually introduce contamination.

Using just a regular test tube, you can see chromium levels that are ten times the upper limit from an individual's normal values. That is just the plain fact that we are surrounded by elements in our environment, in the products and things that we use. So those pre-analytical issues, if they're not followed appropriately, can lead to erroneous results, and affect, therefore, the interpretation and impact on those testing.

It should also be no surprise that in most of the reference ranges and things that we generate in our laboratories are based in patients who do not have implants. So the reference ranges and things that are often quoted are ones purposely in patients who do not have implanted metallic devices because that is the "normal." So then when you do implant the device, we do see values that are higher. That doesn't necessarily mean they're worn or in bad or good shape. That's where we started to look at -- and look at now parsing out just because you have an elevation, well, it could be just because you have an implant. But now we're trying to fine-tune and say, okay, at what concentration or cutoff is significant. And I think the literature there has also shown there's not consistency.

We've talked a lot about also the different matrices that are used, blood being

recommended by the FDA for chromium cobalt in particular because it also helps eliminate some of those pre-analytical processing errors. But the concentration of these elements in the different matrices, blood, serum, urine, and even other things like synovial fluid, are completely different. And there has been data that shows that some of those matrices may be superior in the sense of sensitivity and/or specificity to indicate when wear or other issues might be going with those implants.

But these are all things that I think people need to be aware of because these tests aren't perfect. I don't think we have a perfect test right now to monitor or indicate issues with the elemental issues.

DR. RAO: Thank you.

Dr. Weisman?

DR. WEISMAN: It seems to me that these current tests that we have are only telling you that you've had an exposure to the metal. It doesn't tell you whether there's going to be a complication. That's far too complicated a problem. That's all it's telling you. And that's why Dr. Jacobs doesn't use them clinically, because he doesn't want to know the result because, you know, is it a false positive or a false negative? We don't know. They just tell you that there's been an exposure.

The only way we're ever going to find out, to answer Dr. Giori's question, is really is to have a prospective cohort of joint replacements -- and the orthopedic world has just been unable to get their act together to do such a thing -- where every single patient that gets an implant is going to be followed with objective assessment criteria at intervals over time. Not by the orthopedic surgeon who did the operation; by somebody who is outside that orbit that can ask validated questions about the outcome of that replacement and can assess patients that don't come back. Otherwise, you're just left with, you know, the ones that come back.

So I think that you really need to get your arms around each other and develop this prospective cohort of patients. And I'm not aware that there is one that could accurately satisfy the epidemiologic assessment of Dr. Parks, who would -- who could expand upon this a bit. I know one of my colleagues tried years ago to do this, 10 or 15 years ago, at special surgery in New York, and it was all set up, and it just didn't happen.

DR. RAO: Dr. Giori?

DR. GIORI: So I just wanted to comment or to answer some of those questions. And I agree we don't really have the best cohort or best mechanisms to do that. The American Academy of Orthopedic Surgeons is diving very deeply into registries. And in order to identify and study such a rare, because it is still a rare occurrence, you need to have very large cohorts of people. And so the AAOS is creating and has created, and continues to grow the American Joint Replacement Registry. I don't know if the outcome measures that are being collected by that registry are adequate to answer some of these questions.

There are also large national joint replacement registries in other countries, people -- countries that have socialized medicine, where all of the surgeries all fall under one umbrella and are thus trapped as one. And then collectively, there are registry efforts to combine registries across countries as well. So I think that if you're talking about doing a cohort-type, or a prospective study looking at the effects of joints in large numbers of people, it would have to fall under the area of registries. And the AAOS and other countries certainly are doing that. And it would just be a question of whether the information that's collected in those registries is adequate to answer those questions.

DR. RAO: Dr. Jacobs and then Dr. Connor.

DR. JACOBS: Yeah. I want to echo that. And in fact, an example of that is in the UK, where they have a joint replacement registry, which is pretty mature now. They also

have a cancer registry, and they can cross-reference cancer incidence with joint replacements. That's how we get to the information about whether there's a predisposition to cancer in individuals that have metal-containing implants. We certainly do have a lot of cohort studies in our literature, but the question is: What are we studying and what are we measuring? I agree with you 100% we do need prospective cohort studies to look at these outcomes of interests once, as Dr. Giori has suggested, we have a common definition of what we're looking for, and then do those studies.

Registries are going to be important, but there's also, I think, a role for the National Institutes of Health to help us put our RFAs to help us understand the immune response to metal implants and come up with better testing modalities, because LTT and patch testing are not giving us the answers that we want. They're just not predictive. There's too many false positives and negatives. So we need more advanced approaches to testing particularly with the innate immune system, leveraging the developments in immunology over the last decade.

DR. WEISMAN: Let me respond to that issue.

DR. RAO: Okay. Go ahead.

DR. WEISMAN: In this room with the experts in immunology, if you could wave a magic wand and say, okay, we have all the money in the world, we can set up a cohort, not a registry, but a cohort of patients, that is, every single patient that comes into your institution that either gets an implant or doesn't, right? You get this cohort, and you follow them forward. What measurements would you -- what immune measurements would you put in the freezer? What cells? What tissues? What questionnaires? Whatever it is, what would you put in the freezer to follow over time? Do we have enough information now to even know what to look for? And if we do, let's do it. What would you want to know?

DR. JACOBS: That was the exact question I was going to ask you and your immunology colleagues. I can take a guess at it, but I want to hear it from the experts in this room. What is it that we should be testing, and what should we look for, and you know, where are we most likely going to get the information we need?

DR. RAO: Dr. Pollard?

DR. POLLARD: Easy question to answer. So I think that's exactly the point is that we -- as far as I can understand from what I've read and listened in the last few days, I don't think there's any idea of what to look at. I mean, I think what you would need to do is to actually have some evidence from when you get failures or when you get these adverse reactions of whatever the pathology is. And I presume that that's been done before. And there must be some idea of what's involved in that sort of pathology, what type of accumulations exist, and so forth. But that's at least the end-stage. I mean, that's not going to tell us the beginning stage, but at least it gives us some idea of maybe how to track back.

I wish Dr. Hallab was here. He seems to be the guy that's done a lot of the work in this area. He may have a much better idea.

And is he there?

UNIDENTIFIED SPEAKER: Yeah.

DR. POLLARD: Yeah, can you answer the question, please?

(Laughter.)

DR. YUSTEIN: Dr. Rao, can you just formally recognize Dr. Hallab just for the record?

DR. HALLAB: Yes. Dr. Hallab from Rush University. My travel is paid for by the FDA.

I would be delighted. I just in a way don't know how much more evidence we can provide that -- you know, what have I been doing and publishing that isn't kind of breaking

through.

The correlations are pretty strong between people that have well-performing implants and poorly performing implants when it comes to adaptive immune responses. And then the large-scale studies that have all their practical limitations associated with them because of cost and number of people are always going to be hard to do. But an animal model is really kind of the proof in the pudding when trying to reproduce a phenomenon to see if it's real and so it matter. And both of those have been accomplished, you know, many-fold over.

So the degree to which a risk factor starts to play into the performance of an implant is going to somewhat always be variable depending on the population and the habits, and the socioeconomic status like obesity or smoking. At what level does that matter? But to relegate it to "it's not perfect so we don't need to know it" would be like saying you don't need to know whether somebody is obese or not or whether they smoke because that's not going to impact any kind of surgical planning or preparation.

So I think, you know, other than going through some of the nuances of my talk again, I would invite any kind of specific question that --

DR. RAO: Do we know, Dr. Hallab, if that response that you've measured is a result of an intrinsic response to metal or is it a result of the wear debris that accumulates as a result of mechanical issues with the implants or implantation technique?

DR. HALLAB: So the answer to that would be different in different people. Lucky for us, implant metal debris, be it ionic, and it's generally ionic that creates these more exuberant responses of adaptive immunity that occur over the short-term, innate immunity is something that happens to all of us over the long-term. It's why implants eventually fail at 25 years. It's a subtle response. Well, some people have an exacerbated condition of that that can play into it. It's generally over the long-term that that matters.

And for the adaptive responses, it's something that occurs much earlier. And --

DR. RAO: Thank you very much. And thank you for being available.

Please sit down. Thank you.

(Laughter.)

DR. RAO: And then Dr. Babensee, and then Mr. O'Brien, and then Dr. McDiarmid.

DR. LEMONS: Mine is a response to Panel Question 4. In consideration, my opinion is that consensus standards are needed for preclinical and clinical testing of overall device and debris quantification and biocompatibility. Thus, funding for significantly expanding general interest and clinician, the user, participation is very much needed to provide expertise, balance, and rapidity of modified and new standard documents at this time.

DR. RAO: Thank you.

Dr. Badylak ?

DR. BADYLAK: Yes. Thank you. Although I think the cohort study that was suggested by Dr. Weisman and agreed to by a couple of clinicians would advance our knowledge base and our ability to predict to some extent who's going to be a winner and a loser, there's still going to be a lot of flaws and we may not like all of the answers that we get.

My comment was a little bit more general, and that is that I was thinking of all the different assays we talked about, the LTT and other things. All of these assays basically assess the present-day response to whatever the antigen or material is that you're putting into a Petri dish with cells or perhaps on the skin in a skin patch test, but don't give us the answer we're really looking for in terms of identifying patients at risk, because we're looking at the response of the cells within a standardized assay, a standardized dose, a certain set of conditions.

Each patient, though, with the advent or the advancing acceptance of personalized

medicine, really is getting at our genetic profile, which is behind those cell responses, right? So perhaps we should be thinking about assays that look at those patients that have got, say, genetic signatures that are associated with tendencies towards certain diseases, or maybe even causative of them or associated with that. That way, we can identify those patients that now are the hyper-responders or are not, and also might be able to also account for some of the experiences that each patient has had prior to coming to the surgeon with, you know, at age 49 and needing a new hip.

There are other problems with that, obviously, you know, people's privacy with respect to, you know, their genome and all the things that, you know, go along with that, but at least if we thought about that, we might be able to come up with something similar to, you know, something like a marker or a set of markers like the BRCA2 for breast cancer, something along that line.

DR. RAO: Thank you.

Dr. Yustein, you had --

DR. YUSTEIN: Yeah, I just wanted to follow up on Dr. Badylak's comments there. So would the Panel have any recommendations in terms of -- or thoughts in terms of where we might -- and when I say "we," I don't mean FDA; I mean we as a scientific community -- where we might want to focus our attentions? Earlier some people had spoken about potential single nucleotide polymorphisms in certain areas. I think Dr. Dykewicz mentioned TLRs. Somebody else had mentioned MHC. And again, I'm not an immunologist, but are there -- you know, you got to start somewhere. Are there certain areas where we might want to focus looking for genetic variations that might predispose somebody?

DR. BADYLAK: I don't know how many in the room have experience with, you know, genomics, RNA-seq, and basically, bioinformatics. But with the technology today and

ability to do mass RNA-seq or single-cell sequencing, we can certainly get there. There are known genetic markers of development for the immune system and of responsiveness, and such, and that's where I would start, you know, because there is a database to start with.

But we're talking about something that will take a couple of years, given appropriate funding and the right people doing it. But it might be a way to get us beyond just looking at, you know, a particular response to an LTT.

DR. RAO: Thank you.

Just to move along, we have Dr. Babensee, O'Brien, McDiarmid, Connor, Christian.

Dr. Babensee?

DR. BABENSEE: Yes. So I think that we still need to define what is happening here. And so it seems as though there are three kind of corners to a triangle of the material, the immune system, and immune factors, and the patient, and whatever their factors are.

But I think we should, you know, put together our best explanation from a biomaterials point of view and from an immunological point of view of what is happening, and then, you know, define hypotheses that you can test. And, you know, really, I think, get a good understanding of why things are happening from both the biomaterials and the immunology point of view.

And I agree with what Dr. Badylak said about the bioinformatics. I think there probably exists data that people can use to mine to look for correlations, and things like that. But I think there still needs to be a better explanation from the biomaterials and immunological point of view of what's going on --

DR. RAO: Thank you.

DR. BABENSEE: -- and then define the tests.

DR. RAO: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Yes. I just wanted to sort of -- when I was looking at the question, the question asked us to discuss the status and the clinical utility. And it seems to me, an answer to that question, it sounds to me like for the status, it is not being used in a clinical perspective, generally speaking, for patients. And the clinical utility is up, again, once in the air, even though I have read and seen things about patch tests and LTTs and ELISAs, and other type of tests.

I did want to just ask Dr. Hallab the one basic question, if he or his family members were going in for surgery for an implant, would he do one of those tests prior to that. That was my basic question just getting to the issue from, certainly, from a patient perspective, you want to know that, you know, if there is any potential for that, you clearly want to know it is -- there is potential for me or my family member to have a reaction of those that we've heard in the last several days of various people who have had that because it can have some very traumatic experiences through that, and we want to avoid that as much as possible. So, within reason, if we can define it within and create clinical utility.

And I wanted to also ask, I did not know whether the FDA was requiring to do any of these tests as any of their preclinical or postmarket clinical trials that they're doing so we can get a better assessment as to the utility of it, and should it be standardized as a regular clinical practice.

DR. RAO: Dr. McDiarmid?

DR. McDIARMID: I'm still back on Number 4.

DR. RAO: We're all on that. We're all on Number 4.

DR. McDIARMID: Okay. I'm getting a reverb again. Oh, yours is on.

I would like to talk about metal measures because that is something I know something about. And I just want to -- I heard yesterday the measures are frustrating to

people, and it sounded like frustrating to both clinician scientists, affected patients, but there was some question about whether they could believe the results. And I would like to say that I think the issues are not with the labs, but I completely agree with Dr. Jannetto, that the upstream potential contamination is sometimes what's being measured. And there are ways to standardize collection, and I'm sure his lab gives everybody a handout on how to do this.

At our VA surveillance program, where we follow -- right now, we have 18,000 patients with IED injuries in our cohort -- we have urines looking at 14 metals on 2,000 of them. And I've also followed depleted uranium-implanted patients through friendly fire for 22 years. Matrix issues and collection issues, we've spent the first couple of years really dealing with collection procedures. We measure everything in urine because we had a lot fewer polyatomic interferences that way. We send collection kits to the home VAs of our patients. Everything is standardized. It all goes back to our lab at the VA in Baltimore, and then we've collaborated with AFIP and now the Joint Pathology Center, and occasionally with UPAL (ph.). I don't know if you knew that. And this can be standardized.

And so to the extent that people think that the metal measures are not to be trusted, they are not to be trusted perhaps in the sort of ways that certain people are collecting them, but we can standardize this, communicate this to people, and if you guys are going to do a study, this would all have to be, you know, worked out chapter and verse.

But the good news is, it has been. And this can be done in a reliable way. I think the frustration is that these metal measures do not reliably predict who's going to have a device that fails. And I think too much has been made of 7 ppb, and people get very overwrought about stuff like that. And I get a call at least once a week from a clinician not in our field who's very upset about a value that's outside a normal range. But I hate to tell

you all, occupational limits are way higher than the numbers we're talking about. And so there is a human literature about safe values. Again, it gives you a stake in the sand about sort of where we are in terms of what the clinical interpretation might be.

So I just want to assure colleagues that this is a manageable method to determine metal burden. To the extent that that's predictive or not for the stuff you guys need to know, I can't say that. But I had heard yesterday really wondering whether we could accurately measure these metals, and we can. But there's just a lot of different ways they need to be interpreted.

I'll say two more things. One of the other things that our center does is we have the patients complete a questionnaire, because you can't interpret elevations or excursions for metals especially -- we look at 14 metals, including cobalt and chromium. But people with tattoos, with piercings, and then a bunch of our patients are young men, and they take supplements. You have no idea what's on the internet available for people to take supplements, including cobalt and chromium.

So I'm just saying you can't interpret an excursion if you haven't collected that information. And I'm pretty sure that a lot of orthopedists don't know that, and well-meaning primary care docs, who maybe check this if, you know, between the times your patients come to see you, and they get excursions in these metal values that are probably from something else, or may not be.

But my point is you're kind of flying blind if you're not looking at some of these other explanations. Certainly, serial measures can help you, so getting periodic measures of the same patient may tell you what's going on with their hip. But if you don't ask them did you buy something on the internet and you're starting to take that, or did you get a new tattoo, because as you know, they use metals for the pigments in tattooing.

And then, finally, I would say if we try to do common sense helpful things both for

clinicians and for patients, maybe one of the work products could be some type of FDA guidance on how you actually collect and measure these metals of interest.

DR. RAO: Thank you, Dr. McDiarmid.

Dr. Connor then Dr. Christian and then Dr. Fisher?

DR. CONNOR: Yeah. So I think here, you know, as the statistician on the Panel, estimating rare events is really, really hard, and figuring out how to predict rare events is nearly impossible here. And part of that is just math. Even if these diagnostic tests had 100% sensitivity and 98% specificity, if you have a rare event like this that may occur 1 in 1,000 times, you're going to say no to 19 patients who do fine just to identify one who would, in fact, have, you know, a negative event. So the math makes this really, really hard.

So the question is how to study it and what to do. So I think the cohort idea is, you know, the logical place to start, but it's the wrong place to start just because still we're trying to identify something so very rare. So, you know, we need -- it needs to be studied, but it needs to start with some sort of enrichment trial.

So, for instance, in diabetes drugs, now that you've had to prove after rosiglitazone that their heart is safe, the safety trial is not in the diabetic population. It's in a population who comes in with elevated risk, who's already had a heart attack, who has multiple risk factors. So I think starting with a cohort would be really inefficient, and already there's no one to fund this. So I think that we have to at least start studying with patients who've had, you know, reactions to begin with and look at it in a case control way, which is not, you know, my way -- and correct me if I'm wrong. You're the epidemiologist, and I'm not, but I mean, looking at a cohort, these are so rare, and then to try to predict these rare events seems amazingly challenging to me.

DR. PARKS: This was actually one of the first things I wrote about when I was

putting my thoughts down. You know, there is a tendency now towards developing risk-enriched cohorts, and one of the things I was wondering is, you know, here, we have a substantial number of patients are coming in because they have arthritis from rheumatoid arthritis or lupus-related arthritis. What about those patients? I mean, they already have a constellation of risk factors for aberrant autoimmune response. Perhaps we're not looking at whether they're developing a second autoimmune diseases, but what about a failure of their joint? You know, there are other ways that you can risk-enrich.

DR. RAO: That's a good point.

DR. CONNOR: No, and that was going to be my second idea there. When I, you know, I teach medical students, and one of the things I teach is this idea of how to use diagnostic tests, right?

And I give the example of three people with a positive pregnancy test, meaning, you know, them or their female partner who's sexually active but on contraception is, you know, 20-something-year-olds in medical school, or my sister, who has four kids and wants more. You don't need to do the test on me. If my sister who has four kids and is trying to have another has missed a period, you probably don't need to do a pregnancy test on her. The doctor's prior probability is so influential, but I think so many people just want to look at a diagnostic test.

And the same thing here is -- and so I don't know if this is the answer, but the idea is starting with at least, you know, people who have, you know, a history of autoimmune disease, history of it in the family, so at least to start asking them, you know, before metal implants. And it sounds like that's, you know, probably rarely done. Even the example yesterday of, you know, the gentleman with his chest coming open. It sounded like he had a known nickel allergy and wasn't asked. So just the idea of, you know, starting with, you know, a different level of communication seems to be the key, or at least --

DR. RAO: We have three people who have comments, and then I think we'll kind of wrap it up and try to get an answer to this question. And the three people we have are Dr. Christian, Dr. Fisher, and Mr. Lison.

Dr. Christian?

DR. CHRISTIAN: Yeah. I think what we're all talking about right now is the field of immunogenomics. And we really need to understand the underlying science within that field to get the benefit out of diagnostics as well as a cohort study.

With diagnostics, I think the medical device industry is all for having accurate, reliable tests in the hands of healthcare practitioners to provide the best treatment to their patients. But we're concerned about the limitations that we've all been discussing, the false positives, and the false negatives.

Same thing with the cohort study. If we don't know what variable to look for, there's not going to be much value coming out of that study, and I think Dr. Pollard kind of echoed that we really don't know what to look for. So until we kind of figure some of those things out within that field, I don't think we're going to get much benefit out of these things.

DR. RAO: Thank you.

Dr. Fisher?

DR. FISHER: This goes back to genetic profiles. And where do we start? Dr. Christian and Dr. Parks, I believe, were leaning in -- I thought that they may have had some comments to address where might we start with that. And I wanted to circle back and see if you did have comments on that, where to start, because I may have been wrong.

DR. PARKS: Specifically, on genetic risk factors?

DR. FISHER: Right. Dr. Badylak was talking about that --

DR. PARKS: Well, I was leaning in because -- yeah, I was leaning in because I don't think that you can say, "I don't know what to measure." I mean you can collect the specimens. You can ask the questions in a systematic way, put them in the freezer if you have to, but collect the data. Without the data, you're not going to be able to do the science. And a retrospective study, as nice and efficient as it is, is not going to protect you from recall bias and other sorts of biases if you don't have those exposures and that background information collected upfront.

Now, there's also epigenetics. And we focus a lot on genetic factors, but there's a lot of developmental and epigenetic changes over time, probably even after implant. So I think it's worth keeping that in mind and not just not doing the study because you're not sure what to ask for, you know? We wouldn't do much at all.

DR. RAO: Thank you.

Mr. Lison?

MR. LISON: Wyatt Lison. Thank you. From a consumer point of view and from a lawyer's point of view, I sort of understand from this that the status and clinical utility of the available prognostic tests especially pre-procedure are unreliable. You're getting a lot of false positives, false negatives. But what I hear from people is that they haven't been asked or informed about the right information of, you know, making sure they are not innately allergic to certain metals or that they understand, yes, there are, you know, skin tests out there, but the utility of them are not that good; insurance probably isn't going to pay for them because they're not that good. And I think having that education, that information would help consumers on the front end understand, because I'm sure most people don't know that despite these devices being implanted in them for many years, that a lot of this stuff hasn't had good understand in the front end of knowing when they will fail. They might know what the failure rate is, but they don't have a good

understanding of why they might fail or these unknowns.

And so I think having those sort of issues addressed on the front end would help on the backend avoiding what one of the presenters said, which was going to social media, going to Facebook and fearing the absolute worst and coming to their own conclusions of I have to have this removed because this must be the reason.

DR. RAO: Thank you. I think keep that thought, because that actually would fit into the gap section of the questions, where there's a gap and need for future assessment.

I think, Dr. Yustein, I think we'll take a stab at trying to respond to the FDA Question Number 4, where you'd like some information on the status and clinical utility of the available diagnostic and prognostic tests.

I think there are several difficulties with providing the FDA with any more clarity than we currently have. And the difficulties relate primarily to the need for two or a few different types of information, including the metal component, the immune response component, and the histological response.

There's also the issue of when we talk about the metal testing specifically, there's the whole area of pre-analytical, as Dr. Jannetto put it, or the collection process and how that could impact variations in the results that we get back, and the need for some level of consistency in this pre-analytical processing of laboratory tests.

There's also the issues, again, staying with the metal level responses. There's the issue of a lack of a clear understanding of what is a significant level, particularly given the strong level of occupational exposure, or the levels of occupational exposure that are consistently a little bit higher than what we are currently accepting for metal implant patients.

There is probably even less consistency or agreement on the immune response testing and the validity of the immune response testing, either pre-surgically or post-

surgically. But I don't think the Panel has any additional new information at this point to recommend to the FDA.

There is a desire to get prospective data on any or all of these tests longitudinally in patients who are selected for joint replacements and implant placement. And the goal is that if we have this information preoperatively and then longitudinally have access to the same information postoperatively over an extended period of time, that will eventually provide us better information. There's also a desire to get Federal bodies involved in the process, including maybe the NIH or other Federal agencies, that could help with the collection of this data in a longitudinal format. It's unclear whether the registries will have the depth and the longitudinal survey of these patients over a long period of time to provide those answers.

And, finally, genetic. There is the question of environmental triggers that may predispose some of these patients to developing a heightened response to the presence of a metal implant. I don't think we have data at this time as to say what those environmental triggers may be or what the predisposition of an individual patient will be to develop a heightened response to a metal implant. Is that sufficient?

DR. YUSTEIN: Yes. Dr. Taylor is over there raising his hand. I just wanted to make sure that -- I'm fine with that. I just wanted to make sure if he had anything to add before we close.

DR. RAO: Dr. Taylor?

DR. TAYLOR: I have additional information to provide. I have not had a chance to discuss the testing issues, and I think there are other things holding up lunch, but I mean, you gave a very general discussion. That's fine. But I think some of us have very specific recommendations that I haven't made in terms of testing with that. So we can discuss that later.

DR. RAO: Yeah. I think as a general --

DR. TAYLOR: I mean, it's really critical to discuss the patch testing --

DR. RAO: I'm trying to summarize the entire Panel's thoughts on this issue.

DR. TAYLOR: I mean, the issue of lymphocyte transformation test has been emphasized. The patch testing has not been. The patch testing, there are major issues involved with CDER and CBER. So I think one of the things that really has to be done is CDER dealing with CBER in terms of approving additional allergens. And the other thing is the issue related to patch testing. Patch testing is standardized. It's been around for a long time, and there are multiple allergens that are utilized. The broad utility of it is so much greater that -- we patch-tested with gold. That's how they identified the gold coronary stents, the NIROYAL stents, that produced in-stent restenosis, so that's why -- one of the reasons that they were removed from the market. You can patch test with mercury. There's no lymphocyte transformation test that I know of that does this. So the broad range of substances that can be tested is there.

And I also think the issue is, is who patch tests? So, you know, the lymphocyte transformation has basically one -- well, there are three or four labs that were mentioned by Dr. Hallab, but his is the main one, but patch testing is done by dermatologists, allergists, occupational physicians.

So I think it -- and then the other thing is related of that regarding the Essure. You did come out with a black box warning. Previously, you also -- there was some suggestion of evaluating testing. And I don't know in terms of postmarket testing, so I don't know what's happened with that. So I think that's relevant to the discussion of the testing.

Thank you.

DR. RAO: Dr. Yustein, is that adequate?

DR. YUSTEIN: Yes. Thank you.

DR. RAO: Thank you. I think we are exactly on time for the scheduled lunch break, so maybe this is a good time to stop the questions, and we'll come back to Questions 1, 2, 3, and 5 after lunch. And then we have an additional Questions 6, 7, and 8 related to dental amalgam, and we have a Question 9 on general gaps.

Thank you. We will see you back here exactly at -- should we say 1:40? Is that enough, adequate time for everyone so we can get started? And hopefully, those of us who have earlier flights can get out of here. So let's say at 1:40 we'll be back here. Thank you.

(Whereupon, at 12:51 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:40 p.m.)

DR. RAO: We will now reconvene the Public Advisory Panel meeting. Everyone please take your seats and silence your cell phones. We will continue with the FDA questions now. I think we've done Question 4, Dr. Yustein, and let's move to Question 1 back now. So let's try and restrict the discussion on Question 1 to about 10 to 15 minutes. And if I could, I'd like to get your individual input into responding to Question 1, which basically deals with:

What is the currently available scientific information with respect to the ability of a metal implant or insert to elicit a prolonged and/or heightened immunologically-mediated and clinically consequential inflammatory response?

So there's two aspects to this: One is immunologically mediated, and number two, clinically consequential inflammatory response. What is the ability of a metal implant or insert to elicit prolonged or heighten response?

Anyone that would like to stab at this?

Yes, Dr. Burchiel?

DR. BURCHIEL: Okay. So I'm focusing on the term "validity." And based on the evidence that I've seen, heard, read, and you all have shared with this Panel, I would say -- I have made five points. I'm just going to -- just bullet points. I'm not going to talk a lot.

Obviously, there's local inflammatory reactions, both acute and chronic that are seen, some of those that are related to the surgery itself; others due to maybe the object, the metal. There will usually be a foreign-body reaction or a pseudo tumor, perhaps chronic granulomatous reactions with some metals, not the metals we're talking about today, but you see granulomas in some metals.

Second thing, obviously, you're activating innate and sometimes adaptive

responses, immune responses. We've talked a lot about that earlier.

Third, it's clear we see metal allergies in some people, mostly of the type IV, the delayed-type hypersensitivity, but it may go beyond that, so we had that nice discussion about the different kinds, and you can get a mix of different patients.

Number four, I say you do see -- you may see systemic immune activation, and that depends on a lot of factors. But I'll just throw it out there that there is a consideration you can get systemic immune activation with metals depending upon the metal exposure. And other organs might be affected, such as the cardiovascular system, kidney, and nervous system. We had several people talking about central nervous system effects that they experience. I think they're real.

And then, finally, I said earlier that metals are immunomodulators, not just hypersensitivity agents. They can cause immunostimulation depending upon exposure. So those are my five points.

DR. RAO: Thank you, Dr. Burchiel.

When you talk about the central nervous system activity, how much of that is directly related to metal toxicity and how much of that is a specific immune response?

DR. BURCHIEL: So that's a good point, because in this question, it says separate from metal toxicity, which is an interesting way to think about it. I don't know. I mean, we we've heard a lot about mercury in the brain, but we haven't heard a lot about titanium in the brain or cobalt in the brain or chromium in the brain, etc. So I think it's a difficult thing to sort out. I do know that in inflammatory reactions, you do produce systemic mediators that do activate or interact with the brain and the brain vasculature, etc. So I'll have to leave it at that. I can't say it's direct.

DR. RAO: Dr. Jacobs?

DR. JACOBS: Yeah. I would suggest that based on literature even outside of the

medical device area, that the systemic manifestations of extreme cobalt levels, such as cardiotoxicity, neurotoxicity, and hypothyroidism, polycythemia , those are fairly well-established toxic effects of cobalt. I don't really think you need to invoke the immune system in those responses. So I really think that's separate. I think, though, the systemic effects from these materials or from these degradation products are real, they are documented, and they are associated with extremely high levels, and I don't believe they're immune mediated.

DR. RAO: Okay. Do you have a response to the specific question which talks about the ability of these implants/inserts to elicit a prolonged or heightened immunologically mediated and clinically consequential inflammatory response?

DR. JACOBS: Yeah. I think if by immunological, you mean both the innate and the adaptive immune system, I think it's unequivocal that these implants can do that.

DR. RAO: At the local site?

DR. JACOBS: Yes.

DR. RAO: At the local site?

DR. JACOBS: Yeah.

DR. RAO: And how much of that is related to wear debris, and how much of that do you think is related to metallic implants?

DR. JACOBS: So I think the majority of the chronic inflammatory reactions are related to the degradation products from the implants, whether they be metal ions, particles, metal protein complexes, and all other bunch of moieties we haven't even discussed.

DR. RAO: Okay. Thank you. Thank you very much.

Dr. Giori?

DR. GIORI: I think that the corrosion is one of the major issues right here. I think

that it falls under what Dr. Jacobs was already saying. But when we're talking about wear, that would be particles that are just generated from two bearing surfaces rubbing against each other, but one of the major concerns right now for us is corrosion products.

DR. RAO: And you think these corrosion bodies are contributing to a local --

DR. GIORI: Yeah. That's ALVAL, so that's already been described histologically, so it's an immune-mediated local reaction.

DR. RAO: Thank you.

I'm just not seeing the enthusiasm I saw for Question Number 4.

DR. YUSTEIN: Dr. Rao, Ron Yustein. So can we take it the next step further? What do people think in terms of -- you know, it sounds like people are confident in terms of the local response, innate, adaptive, etc. What is the data telling us in terms of the likelihood or the possibility that that can then transform into a more systemic thing?

You know, looking at the list of symptoms that Dr. Fisher showed during his presentation yesterday, patients noting complaints of, you know, fatigue, cognitive issues, muscle ache, various joint ache, weight loss, various systemic type of things. You know, back in the day, not too long ago, we used to use interferon to treat hepatitis C, and a lot of those side effects were consistent with a lot of those side effects were consistent with a lot of those symptoms.

So if, you know, we go back to Dr. Hallab's slide and Dr. Santambrogio's slide, where they showed a lot of the actual biochemistry within the cell, with the inflammasome and all the interleukins and cytokines and interferons that got produced during the innate process, is it possible that we can see symptoms like that stemming from, initially, from a local innate response, if that makes sense? Is it possible? And if so, what might be some of those system signs or symptoms that you would say, yeah, that could reasonably be a consequence?

DR. RAO: So the question really is: Can we attribute systemic symptoms, not local, but systemic symptoms to some extension of the local inflammatory response and the local immune response?

Dr. Burchiel, you had your hand up, and then Dr. Weisman?

DR. BURCHIEL: Yeah. So, again, I'm not going to argue, but the immune system, when you have elevated circulating cytokines and the like, they're going to do this. They're going to have CNS issues. I'm not saying it's going to cause the muscle tremors or some of the other things, but fatigue -- and I'm glad you brought up gamma interferon. A lot of these cytokines have surprising effects on the brain, and they do get into the brain, and they do activate the central nervous system. So I don't think we have to go too farther. I'm just saying, clearly, when you have a major chronic inflammatory situation, with cytokines being circulating, circulating in the blood, they're going to affect the brain as well.

DR. RAO: Dr. Weisman?

DR. WEISMAN: Correct me if I'm wrong, but fatigue and pain are the reasons why the patient sees the orthopedic surgeon for a knee or hip replacement to begin with. So I'm not surprised that some of those symptoms persist, because it's not a perfect solution. It's a really good one. And pain may or may not be related to the procedure. There may be other aspects of pain that are involved. So I don't see how you're going to be able to connect these, connect the local response to what are longstanding systemic issues. That doesn't make sense.

DR. RAO: Dr. Fisher?

DR. FISHER: Just real quick. So Fisher, FDA. So that's a patient coming in for a joint replacement. Once again, I fall back on the example of a gynecologic device insert, patients going in feeling fine, going in for an elective procedure, and then comes out with

a whole spectrum of symptomatic symptoms, fatigue, and those.

DR. WEISMAN: Are you discounting the fact that the device was there to generate an inflammatory response --

DR. FISHER: No.

DR. WEISMAN: And, hence, then produce a temporary -- produce the temporary effect of, you know, inhibiting -- well, it's a temporary contraception effect. And all the issues involving those issues in women may remain, and you know, could persist, or other issues could come up. So I don't see how, unless you know ahead of time that you have the tools to be able to sort these preimplantation issues out to begin with and see how often they're resolved or how often they occur with other methods of contraception, for example, not an implant, but after women get another form of birth control that's not in implant, unless you do those kinds of studies. How do you know?

DR. YUSTEIN: We are doing it, yes, and that is a study that actually is being done by the Essure people. But I guess -- and again, I don't want to belabor a point, but there are some people out there who believe that, you know, you can generate this local response, and perhaps in some patients, they generate an exaggerated response, and maybe that exaggerated response is prolonged because they're continuing to be exposed to the metal implant. The insult isn't being taken away. And so could that chronic, ongoing local inflammatory response lead to more systemic symptoms that the patient wasn't having before?

Again, there's a host of responses. And a lot of it, some people have said, mimic chronic fatigue syndrome or fibromyalgia, those general types of symptoms. And we're just trying to ask the Panel is it biologically plausible based on what we know about the science of what goes at the innate and adaptive cell response level, is it biologically plausible that that can happen.

And what I think I heard Dr. Burchiel say, yes. And I think what I'm hearing Dr. Weisman say is no.

DR. WEISMAN: Well, if you're asking about the triggers for a pain amplification syndrome like fibromyalgia, help me out where -- help me out. If you could figure that out, the two of us will get the Nobel Prize together. I mean, that, you know, this is -- it's very difficult to be able to relate any of these things to the onset of a pain amplification syndrome.

DR. YUSTEIN: Okay. So maybe fibromyalgia isn't the only example. So, I mean, the symptoms that we're being told by patients with various devices, and I think you even heard Dr. Tower say that he would -- you know, on hindsight that he was also seeing it in some of his hip patients -- were things beyond pain, you know, things like chronic fatigue, various joint pains, and not just the joint where a surgery may have been done, because you know, even the Essure women were complaining of low back pain, cognitive difficulties, hearing changes, hair loss, teeth falling out, you know, just a whole set of symptoms and signs that would have -- that are more indicative of systemic things, weight changes, mood disorders, those kinds of things.

So I don't want just focus on pain. And I'm just saying -- I'm not necessarily saying, you know, let's go through each symptom and say yes or no, but is it biologically plausible that this can happen and that patients may manifest with these various systemic types of things. Whether it's these three, those four, these two, I don't know. It goes back to a prior question that we really don't know what --

DR. RAO: Just to interject, though, just to interject, Dr. Yustein, I don't know that his presentation made it clear that he was referring to an immune-type response.

DR. YUSTEIN: Correct.

DR. RAO: He was referring more generally to a metal response rather than an

immune response.

DR. YUSTEIN: Right. So maybe I gave the wrong example, but we heard the woman talk about the IUD patients. We heard the Essure groups talk in the past. So we're kind of using that as kind of a, you know, is that biologically plausible.

DR. RAO: So let's break it up into two parts. Is there a potential immune response that can explain these generalized symptoms? Anyone?

(No response.)

DR. RAO: Well, I think that itself is an answer.

How about is there a potential metal -- did you have something to say, Dr. Parks?

DR. PARKS: Well, originally, you said a localized immune response, so --

DR. RAO: No, we moved to a systemic.

DR. PARKS: If you're talking about systemic, I mean, there are --

DR. RAO: We are talking about systemic.

DR. PARKS: -- examples of people having systemic inflammation that, you know, may be associated with developing depression. I mean, I think it's really hard to tell, and I think that's partially what you were saying, so -- but I think, biologically, perhaps --

DR. RAO: It's feasible?

DR. PARKS: It's feasible.

DR. BABENSEE: Yeah, could I answer --

DR. RAO: Dr. Babensee had her hand up, yeah.

DR. BABENSEE: Yes. Yes, so I would believe that it is possible especially with elevated cytokine levels that you could have those kinds of problems. I think the other thing that really supports that is I think yesterday some of the patients were saying that when the device was removed, these symptoms went away. So I think that is a strong indicator that it was device-associated.

DR. RAO: If that's what you think, Dr. Babensee, could you propose a mechanism for that where you might want the FDA to explore that a little bit further?

DR. BABENSEE: Well, I would say with chronic inflammatory stimuli, whatever that might be, if it's wear debris or, you know, particles, or ions being released, but whatever chronic inflammatory stimulus causing, you know, activation of the leukocytes, releasing the cytokines that are, you know, known with inflammation, and those do have effects on organs and the CNS, and other things, to cause --

DR. RAO: And what specific testing would you recommend to explore that avenue? Is there some way you --

DR. BABENSEE: Cytokine levels.

DR. RAO: Cytokine levels? Any specific cytokines you can think of?

DR. BABENSEE: IL-1, IL-6, interferon -- gamma --

DR. RAO: And you would correlate that with what?

DR. BABENSEE: Well, I think we're just saying whether the patients have certain issues that come up with the device implant.

DR. RAO: Dr. Parks, do you have anything to add to that?

DR. PARKS: I mean, you're looking at symptoms. You would correlate it with symptoms. You might do it pre- and post-removal.

DR. RAO: Dr. Badylak and then Dr. Weisman?

DR. BADYLAK: Yeah, I agree with Julia. It certainly biologically possible. The bigger question, though, is whether it's related to the metal itself or just the presence of something there causing chronic inflammation. So you can't really -- you know, and that study is a little bit more difficult. It's doable. Part of the problem with these things, of course, is a lack of a good animal model, where you could, you know, put these things in, because you can't evaluate some of the subjective symptoms that we manifest as humans.

But you can certainly assay the pro-inflammatory cytokines that Julia was mentioning, IL-1 beta, IL-6, and so forth. But it's definitely biologically possible.

I think for the FDA's standpoint, what they want to know, if somebody comes to them with the next device, is it, you know, is it because of the composition of it or the simple fact that you're going to cause inflammation. And if it's an intrauterine device, now you're really stuck, right, because that's what's causing the lack of conception or lack of embryonic development, because you have a site in the uterus that's chronically inflamed. It's the point of the therapy and yet it's the cause of the symptom. So maybe the better thing is to identify those subset of patients who simply can't use that method of contraception.

DR. RAO: Dr. Weisman?

DR. WEISMAN: Well, the story about how if you remove the intervention, the implant and the testimony that "my symptoms went away," that's not very powerful or convincing to me, because what we do know is when there have been situations when there's been an environmental trigger, such as the drugs -- a lot of drugs that are used, you know, 20 years ago, high doses of certain drugs, caused lupus reactions, right? When you stop the drugs, a good percentage of those lupus reactions did not go away, right?

And so we also know about the grapeseed oil epidemic in Spain, and we know about the altriptophan epidemic in the U.S. We know about the gadolinium issue. We know all these things when there was a big insult, symptoms emerged, and most of the time they did not go away, you know, when the thing was stopped. So it's not -- that's really not good evidence, you know, that there's a cause and effect there. So I just want to bring that up when you deal with these issues.

DR. RAO: Dr. Connor?

DR. CONNOR: Yeah. So, I mean, I agree that, you know, it's anecdote, but at the

same time, I don't want to be that quick to dismiss it. You know, FDA endorses and I've designed, you know, numerous randomized withdrawal trials for drugs that I get, you know, an insult can be persistent. But in randomized withdrawal trials in psychiatric drugs, and such, we take patients who respond to a drug, randomized half to stay on and half to be removed from the drug, and the idea is if I can cause improvement and then take it away when I take the drug away, that's really strong evidence that the drug is having its intended purpose. So, here, it's different. But, you know, I get that some effects could be persistent even if you remove it, but I don't want be that quick to say that that's not evidence. That could be stronger evidence to me, and --

DR. WEISMAN: Well, what I'm talking about are not withdrawal studies. What I'm talking about is --

DR. CONNOR: Well, but I think it's the same phenomenon, potentially.

DR. WEISMAN: You have a normal person, doesn't have lupus or rheumatoid arthritis, right? You add the insult, triggers it; you remove the insult, the problem remains. And a certain percentage of that, those are the ones that -- that's what I'm talking about. It's a very complex story about why those things happen.

Your example is you've already got the disease, on the drug, and then --

DR. CONNOR: No, I agree that it's complex. But I'm just saying I don't want to be quick to dismiss the idea that removing it and removing symptoms, that can't be it. I mean, I think the issue is people aren't listening to patients enough. And I get that it's really complicated, but being rapid to dismiss, you know, that mechanism, I don't know.

DR. WEISMAN: Well, I've dismissed it as powerful evidence, as was proposed, you know, to support the notion that the intervention caused the problem. I gave you known examples of where the evidence is not powerful. Okay. That was my --

DR. RAO: Thank you, Dr. Weisman.

Mr. O'Brien?

MR. O'BRIEN: Yeah. Just to follow up, I may have conflict with "scientific evidence." But clearly, anecdotally, as we heard -- but also, you know, when Dr. Weaver was going over terminology, I mean, we have a classification of patients that we call RTCS, ready to commit suicide. I mean, these are the patients that are not having general localized issues only. They're having vast, global issues that are fatigue and cognitive issues, et cetera, that when they do take their instrumentation out, by and large, the majority of them do dissipate. Not all of them, but a vast majority of them. So it's anecdotal, but it clearly does exist.

DR. RAO: Thank you.

I think, Dr. Yustein, we're ready to come up with some kind of consensus statement.

DR. YUSTEIN: Sure.

DR. RAO: And the question pertains to the scientific plausibility of either a prolonged or heightened immunologically mediated and clinically consequential inflammatory response. And I think the Panel generally feels that a local inflammatory/immune response clearly occurs. There's also some question that a systemic immune response may occur, but it does not appear that we have either the scientific weight of evidence to make that certain or a scientific process that would clearly help us understand the mechanism a little bit better at this stage. Given the clinical anecdotal evidence that we have received as a Panel, and based on our individual experiences, this may be an area for future study down the road.

Is that adequate?

DR. YUSTEIN: Yes. Thank you, Dr. Rao.

DR. RAO: Let's move on to Question 2, and again, let's try and discuss this for 10 to 15 minutes.

And Question 2 relates to patient-related factors based on scientific information that we believe may increase or decrease an individual's susceptibility to this response to a metallic implant or insert. So this is related to patient-specific factors that may change the individual's susceptibility to a metallic implant. And there's a number of patient-specific factors that the FDA has given us as examples, including gender, age, reproductive status, medical comorbidities, including preexisting autoimmune disorders, modifiable behaviors, smoking, tattoos, metallic jewelry, and the location of device implant and duration of implant.

Anyone that would like to take a stab at this?

Yes, Dr. Suzuki?

DR. SUZUKI: I'll just begin more broadly, but specifically applying some of the knowledge that we know about dental implants and perhaps apply some of that information to overall metal implants as well. But, certainly, there is -- on this list, I agree with everything about senescence and aging and perhaps higher risk for implant failure because of just the lack of systems operating as they were when they were 26 years of age.

And also, I agree with the other comorbidities, for example, connective tissue diseases. The American Academy of Periodontology has now raised the specter of -- or the question about connective tissues diseases related to the success of metal implants osteointegrating.

What's not on this list, however, are some of the medication factors that are now being recognized for contributing to the failure of dental implants. For example, we now recognize from the Buffalo Osteo Health Study that osteoporosis plays a very, very big role in dental implant failures. There are many family of medications, steroids, anti-cancer drugs, thyroid preparations, cyclosporine, even publishing in *JAMA* recently, antacids, all

can contribute to osteoporosis; in turn, may have an impact on this implant failure, too.

DR. RAO: Is that secondary to an immune process or is that secondary to a mechanical process?

DR. SUZUKI: It's not known if it's immunological or if it's mechanical, but clearly, the associations of these medications have been recognized. And actually, more recently, even the family of drugs called selective serotonin reuptake inhibitors, commonly called antidepressants are contributing in a major way to dental implant failures. So those are some of the risk factors that are not on this list that I think need to be explored and perhaps even a retrospective study to look at not only dental implants, but all these implants can be at least considered.

Another factor is IV and oral bisphosphonate drugs, which dramatically alter the bone metabolism that our colleagues around the table know. And that needs to be explored also, and not just for dental implants, but for all implants: What is the effect of that medication?

DR. RAO: Thank you.

Anyone else with patient-specific factors? Yes, Dr. Lemons?

DR. LEMONS: The list and the latter -- excuse me -- the latter two items, location of the device implant and tissue interface and duration leads to a comment, sort of a response, and that is analyses of local site-specific biomechanical force transfers and alternation of tissue-to-device interfaces over function and time often influence elemental transfers. Well-known. Thus, what are the influences of the functional conditions at that device-to-tissue interface? I think that needs to be included in any of these assessments. Very different, one to another, very patient-specific, very specific. And as we move, like said in dental implants, to different conditions of use, we're expecting a significant change in outcome.

DR. RAO: Dr. Jacobs, Dr. Giori, from an orthopedic perspective, any patient-specific factors that may change their response to a metallic implant? And let's initially try and restrict it to an immune response locally, and then you can expand on that if you'd like.

DR. JACOBS: Yeah, the only factor that I've seen fairly convincing scientific evidence, patient-related factor, probably is gender. And there is fairly good information, for example, in the metal-on-metal literature that females have a higher rate of failure. It's complex. It may not just be immune-mediated. It may be based on their pelvic anatomy and the placement of components and preferential edge-loading. Nonetheless, there is a higher rate of these adverse local tissue reactions, which are immune-mediated in women with metal-on-metal total joints. The other factors are less well supported.

DR. RAO: Thank you.

Dr. Giori?

DR. GIORI: I have nothing to add to that.

DR. RAO: Dr. Christian?

DR. CHRISTIAN: Yeah, I'll mention this. I think this is related to patient factors, and we really haven't discussed this at all, but the stochastic nature of the immune system. Dr. Badylak may have been touching on this earlier in terms of we all have T-cell receptors, but they are different, and how those are generated is through a very random process, and that is playing into some of the effects that we're seeing here in terms of patient variability.

DR. RAO: Could you expand on that just a little bit, please?

DR. CHRISTIAN: Sure.

DR. RAO: Dr. Suzuki, if you'd turn your mic off --

DR. CHRISTIAN: What I'm referring to is VDJ recombination and how the receptors that are interacting and playing a role in type IV hypersensitive -- formed, and how they

modulate the response. So there is some bias in terms of the T-cell receptor repertoire, and you would wonder how is the immune system designed to respond to all the different types of pathogens it could possibly interact with, and if we see some bias, some commonality in these receptors. And it is hypothesized that that has to deal with some cross-reactivity. So some receptors can cross-react, and I think that's why we see people with several different metal allergies and not one specific to nickel.

So the way that the immune system is developing its receptors is a very random process, hard to predict, and maybe put patients into bins. But, again, this is an area of science that we don't know a lot about right now. And referring back to Question 1, we really didn't talk about the gaps, and I think this is one of them in terms of how the T-cell receptor DNA sequence plays into antigen specificity.

DR. RAO: Thank you, Dr. Christian.

I think we're ready to take --

DR. YUSTEIN: Can I actually --

DR. RAO: Please go ahead, yes.

DR. YUSTEIN: Sorry about that. I'm going to push just a little bit further. Can we talk a little bit -- and maybe there's not much more to say -- about location. And let me just say something -- and again, I'm not an immunologist, but I stayed at Holiday Inn Express last night, so I've done some reading -- my understanding is that the immune system is not just --

DR. RAO: That's one reason they used to have these meetings at the Holiday Inn.

(Laughter.)

DR. YUSTEIN: Yes. Yeah, I used to stay there. I stayed there too much.

So my understanding is that the immune system really isn't just an immune system, that it's kind of like the United States. We're one country with 50 states. And similarly,

the immune system varies from organ to organ, so even within my understanding, even within the female genital tract, the types of immune cells in various locations, whether in, like, the lower third of the female genital tract that's closer to the vagina versus further up near the fallopian tubes, the actual types of cells and the percentage of different cells in those different locations varies.

So getting to the location of device implant -- and the answer may be we don't know, and that's okay, but I just want to put it on the table -- does the location of device implant matter in terms of, or could it matter, in terms of whether it's contact with endothelium, epithelium? Somebody earlier today said, well, maybe we're seeing differences between metal-on-metal hips versus spine. I think it was you, Dr. Rao, because the one is in a joint, where it's maybe less vascularized versus the well-vascularized spine area. I'm not an expert in that area. But is there anything else we know -- and again, the answer might be, no, we don't, but it's possible -- in terms of can the location of the implant elicit perhaps different degrees of responses? Again, I'm not an immunologist. I'm just throwing stuff out there from reading. So --

DR. RAO: Dr. McDiarmid, from an immunological, toxicological --

DR. McDIARMID: I'm not the immunologist, so I don't think I should answer that question.

DR. RAO: Dr. Weisman?

DR. WEISMAN: Well, it doesn't really matter where the foreign antigen is placed as long as there's access to the bloodstream. I mean, you know, as long as there's access to the immune system, would it really matter -- if you're talking about an immune-mediated response, right, would it really matter? I mean, in the old days, you have bugs on a heart valve or you have bugs on a ventricular atrial shunt that, you know, would cause an acute and a prolonged immune response, right? I'm thinking of things that happen that we know

about, right? These are known things; when there's organisms there, there's an immune response.

Other parts of the body, the GI tract, where there's a lot of organisms, are there immune responses? Yes. You know, there are immune response to -- in fact, you can even detect in an infected joint, for example, you might be able to detect in the bloodstream some small particles of DNA that can identify what the organism is. There's some current research going on there. So I'm not sure it really matters where it is as long as you have access to the bloodstream.

DR. RAO: Thank you.

Dr. Burchiel and then Dr. Babensee.

DR. BURCHIEL: Well, I kind of agree and disagree. It does matter where you put it. The gut is a tolerant organ. There are immune cells throughout the gut, throughout -- there's a lot of work, and you're talking about the microbiome now, which was a lot of work going on, and what role they play even in metabolizing metals. I mean, that's part of the whole issue. We heard a little bit about that yesterday, I think.

So where the devices go does make a difference. I think we'd have to agree with that. There are immunologically privileged sites like the eye. There are other places, too. But not all are readily available, not all are good places to put an antigen or to put a chemical, any kind of foreign chemical. So I don't think we know a lot about it. I'd be hard pressed to say how could we prove that, you know, without doing something in an animal model, obviously, which we all agree we don't have good animal models to assess most of these types of conditions.

So I would just be a little bit careful about that, about thinking that anywhere in the body it's going to be -- if it gets in the blood -- oh, the other point I wanted to make was, you know, we have every imperfect -- when we -- as I do studies in people, and I do

environmental exposures to metals, and I take blood, that's not really the best place to get your samples to assess your systemic immune system. We do it. You can measure cytokines and antibodies, but those cells are all in transit. They're going either from the bone marrow -- they're going from a primary lymph node organ to a secondary lymph node organ. They're the highways of your body, right? So I think that's imperfect. But we can't go in and poke around and take a little bit of this and a little bit of that from all of our, you know, study populations, so we have some limitations along that.

I would say that there's a lot of trends in pharmaceutical research today and in preclinical research today about using humanized animals. And there are humanized mouse strains and genetic mouse strains. They're not perfect, but they can reconstitute certain areas in which you can do -- or even going beyond putting metals into cell lines and culture, which I hate -- that you can actually do, you know, the studies on a chip with complex cells, where they're looking at things together. I'm not trying to start a whole new field of work there, but these are -- they are improvements. Whether they're worth the investment, whether they're going to pay off for prosthesis and for the metal sensitivities and immune stimulation, I don't know the answer to that. That's a gap.

DR. RAO: Dr. Babensee?

DR. BABENSEE: Yes. Sorry. I think you're correct in saying that different locations have different immune cell populations. I think that also, you know, can explain immune-privileged sites. But I think in the case of the gynecological tract and the uterus, it really depends on the purpose of those locations, that the uterus is meant to accept and not reject a fetus, which is not genetically identical to the mother. And I like the idea of the kind of doing organoids or organ on a chip to kind of maybe try to maybe understand what could be happening in different sites, because, you know, there are certain sites that you could get access to, like, things that have sort of a synovial lining like the spinal cord or the

knee joint. You can make sort of an air pouch and put particulates and test things in there and then sample out of this subcutaneous air pouch that has a kind of pseudo synovial lining. But it is difficult to get. You'd have to do the tissue samples, and then do cytokine assays on those tissue samples.

DR. RAO: Just a quick comment, Dr. Taylor and then quick comment, Dr. Dykewicz, and Dr. Fisher, and then we move on.

DR. TAYLOR: Regarding patient factors, you know, it's been shown, at least clinically, that some patients that have had orthodontia prior to having their ears pierced or any piercing actually become tolerant to nickel. So that's a potential patient factor.

The other thing is, is that nickel sensitivity is frequent. I mean, it's 15, 20% of patients that are patch-tested in the general population. And it may vary from, you know, up to 5% or more. So in that regard, instituting the regulations that the European Union have on release of nickel from devices I think is something that -- I know -- I've been involved with the American Academy of Dermatology with this and the American Contact Dermatitis Society, who recommended this for years. We met with the CPSC. We've met with other groups that try to institute that. That has shown to reduce the prevalence of nickel sensitivity. Whether that would have an effect on implants, I think, is a question, but it's something that's almost a no-brainer.

The other is, you know, contact dermatitis or the patient reactant can be localized -- so there are three variations of this, localized, the sort of regional, and then disseminated.

And other thing, the last point, is in terms of location, I think it's really important the FDA look at the different devices. We've concentrated on orthopedic and we've concentrated on gynecologic, but every organ has got them. There are tons of devices. And looking at the registries and what -- pick out of the registries their defects and

problems with those. But I think looking at those groups that have high volumes of patients with those specific implants that have registries would give some advice. The other is static versus dynamic. Again, static, so the Nuss bars, I think, potentially, I think are more likely to produce reactions, and testing in advance might be predictive or semi-predictive. Otherwise, it's generally not predictive.

DR. RAO: Thank you.

Dr. Fisher, you had a comment?

DR. FISHER: Yeah. Just at the risk of oversimplifying the issue about location, with hips, we see pseudo tumors that are formed there. So, you know, from my perspective, what I was wondering was if you took the same material and you put it in the knee, if you put the same material in a shoulder -- both of these are articulating joints -- would you think that you would see pseudo tumors form there? So, you know, I didn't mean to overthink it. I'm just wondering, you know, is it the device material, doesn't matter where you put it, you know? If you don't see pseudo tumors in other locations, is there something else to explain it? Thoughts?

DR. RAO: Dr. Giori, you were going to say something?

DR. GIORI: Yeah, I think that the main difference between the hip and perhaps the knee is not just -- it's not really just the location, but also the forces that are being transmitted across the joint and the design of the implant. As I mentioned before, a knee replacement doesn't have a modular taper junction, doesn't have the opportunity to have mechanically assisted crevice corrosion, and so I think the degree of corrosion that happens in a knee replacement is going to be far less.

I think that if somehow you manage to generate the same sort of ions that were -- or metal ions that were coming out in the knee versus the shoulder, or something like that, in some way, I would imagine that you would have the same type of response. But I

think that it's not so much a location-specific, but rather the mechanics of the joint and the design of the implant that --

DR. RAO: Thank you.

And, Dr. Dykewicz, you had a quick comment?

DR. DYKEWICZ: Quick comment is to just be cognizant of mucosal-associated lymphoid tissue, which constitutes about 50% of lymphoid tissue in the body and would be more localized in mucosal areas, including vulvovaginal area, potentially, the oral region, you know? There's the bronchial-associated lymphoid tissue, gastrointestinal-associated lymphoid tissue. So depending on whether there's some mucosal surrounding, that could make a difference.

DR. RAO: Dr. Jacobs, could I ask you just for a quick comment so we can wind this down?

DR. JACOBS: Yeah, I would agree with Dr. Giori that why we're seeing more pseudo tumors in the hip has more to do with design. In fact, there are pseudo tumors reported in the knee when you do have the same kind of modular implants, like for revision knees, that generate a lot of tribocorrosion debris. So I don't believe that there's anything intrinsically about those locations that's going to result in a different local reaction.

DR. RAO: Dr. Babensee, you had your hand up?

DR. BABENSEE: Oh, yeah, I was just with Dr. Giori, the idea of the location mattering, and it's also the extent -- I would just add to what he said was the chronic inflammation generation --

DR. RAO: Thank you.

I think, Dr. Yustein, in regards to Question 2, the Panel generally feels that there are some patient-related factors that may affect the local response to the implant, and possibly the systemic response to the implant. Some of the local factors that may play a

role are mechanical factors, including osteoporosis, which may impact in a combined kind of way, medications, age of the patient, gender factors, such as mechanical changes in the bone, anatomic changes. There are also some local factors that may play a role because of their different biome contents based on their exposure to the exterior, either the GI or GU systems. And then there are, finally, potentially systemic immune responses that may be patient-specific that we don't have a good handle on as yet.

Is that adequate?

DR. YUSTEIN: Yes. Thank you, Dr. Rao, and I'll try to be quiet during Number 3.

DR. RAO: Let's move to Question Number 3. And Question Number 3 relates to device-related factors, implants or insert-related factors which may play a role with a patient's heightened or prolonged response to a metal implant or insert. And specific device issues include: metal alloy compositions, coating characteristics, manufacturing processes, or corrosion/degradation products.

And we'll start with Dr. Jacobs and Dr. Weisman to follow that.

DR. JACOBS: One of the experiences and one of the things we've observed when we were talking about tribocorrosion of modular junctions in metal devices is that although both -- the two major alloy systems are titanium alloy and cobalt chrome alloy. Although both systems will show tribocorrosion at those interfaces, the adverse local tissue reaction seems to be primarily reported in association with cobalt chrome devices. So from that we infer that there's far more reactivity to cobalt chrome than there is to titanium debris. And that might be by virtue of the fact that titanium is far less soluble. But there may be other characteristics as well. And that's the rationale for avoid cobalt alloy heads in total hips and using them -- and having a cobalt-free reconstruction in total hips to try to mitigate that problem.

DR. RAO: Thank you.

Dr. Weisman?

DR. WEISMAN: I have a more general question. Are we still talking about dental amalgams in these discussions?

DR. RAO: We're coming to dental amalgams after this.

DR. WEISMAN: Okay. That's --

DR. RAO: So if we can get through this, we're going to go to dental amalgams.

DR. WEISMAN: Right. I just wanted to -- that's been particularly absent in the discussion.

DR. RAO: No. Because they've kind of stratified the --

UNIDENTIFIED SPEAKER: Six through eight.

DR. WEISMAN: Because there was a bit of skipping around. That's right.

DR. RAO: Oh, sorry about that.

But any other devices-related factors?

Yes, Dr. Babensee?

DR. BABENSEE: So I put down the composition of the device, the percent chemical composition, you know, the microstructure of it, the effect of the manufacturing process. And any --

DR. RAO: And could you just explain how each of these things may impact the response?

DR. BABENSEE: Well, there were some cases -- there was one slide we saw yesterday where there were, like, maybe four or five metals, and different parts of it were made out of different metals or some were coatings, and so it gets very complicated. People don't know what's in those devices that they're getting. So what is that composition? What is the chemical, the percentage of each? What is the effect of manufacturing process? Because, you know, things can -- the structure can change

depending on that. Is there any coating? There was an example of carbon coating mitigating the effect of the metal exposure. So I would say those types of things.

DR. RAO: Is there a thread to any of these assorted facts that you can help the FDA with? Is there one thread that stands out consistently?

DR. BABENSEE: There needs to be reporting of what the device is made of.

(Applause.)

DR. RAO: Dr. Jacobs and then --

DR. JACOBS: Yeah, I think the one thread I would say is it's related to the amount and type of degradation debris from the implant. And those implants that are far more resistant to corrosion and wear are going to generate less debris and be far better tolerated.

DR. RAO: Dr. Connor?

DR. CONNOR: Yeah, I was going to ask this to FDA, and we ran out of time this morning, but is it accurate that everything that is included in an implant isn't always included on the label? And part two of that question is do you do any sort of testing, or anything, to ensure that, you know, every element that is included, that a sponsor says is included is, in fact, there, and there aren't extra things?

DR. RAO: Dr. Yustein, do you have an answer to that or --

DR. YUSTEIN: That's kind of a trick question, Dr. Connor. So it's not uncommon for a labeling to describe a device as a stainless steel device, okay, but you may not know that stainless steel is composed of multiple different individual elements.

DR. CONNOR: Right. And I guess the reason I asked, like, I have a mushroom allergy, and both days at lunch, I ask if the meatloaf sauce had mushrooms, and it didn't, but yesterday's beef did. And I know to ask that.

DR. YUSTEIN: Right.

DR. CONNOR: And if a patient even with an allergy, you know, they can look at the label, and the doctor may not even know to call the sponsor, right? The surgeon can probably only look at the label. So I guess that's what I'm asking. Like, how hard is it? I got to ask the chef. A patient and doctor may not be able to ask the guy at the factory.

DR. YUSTEIN: Right. Let me see if there's anybody on the frontline reviewers that wants to take a crack at that.

Okay. Ms. Goode is going to take a quick crack at that.

MS. GOODE: Jennifer Goode, FDA. So we do not commonly require manufacturers to disclose in the label all of the materials that are involved in the composition or manufacturing of a device. However, some manufacturers of devices routinely will put that information in their label. There are some kinds of devices where some of that information is included but not all of them. If a device is identified as having something that there may be a potential concern with, but the benefit/risk is such that we think the device should be on the market, we may ask that something be included in the label. And so as Dr. Yustein was pointing out, in the past, we may have said stainless steel. There may be some groups that now actually identify the major components of stainless steel, but it's not routine across all of our devices.

DR. RAO: Thank you, Ms. Goode.

Dr. Lemons, you had a question?

DR. LEMONS: Looking at the list and the Question 3, I think it's fundamental that we have this type of information to ask to sort of answer those questions that we have been considering in terms of the response, immunological response. So I wrote a brief comment about this, which I'll read.

"Considering the many different applications of metallic biomaterials, what are the site and condition-dependent specific organometallic complexes that form? And from a

systemic perspective, how are these compounds transferred as related to dose-response time reactions?" We need to know that. So the answer is we need this information and we need the specifics of how it's transferred.

DR. RAO: Dr. Badylak and then Dr. Burton?

DR. BADYLAK: Yeah, so I think to the extent possible, all of the composition should be listed for the reasons -- I thought that was an excellent example of the mushroom allergy. And all of the things listed obviously will affect the patient's response.

So I'm thinking of this from the FDA's standpoint. How do you evaluate those things? And one of the things that FDA is going to be challenged with over the next couple years, perhaps are already, is probably one of the hotter areas in biomaterials called immunomodulatory biomaterials, which is basically recognizing that now there are pro-inflammatory and anti-inflammatory modulators of the patient response. And you could take something that might be very egregious to put into a particular location, but if it's coated with certain things that totally changed the way the patient responds, all of the sudden, it becomes acceptable.

And one of the, I think, questions that's going to have to be addressed in terms of whether it's CDER or CBER is, you know, are we talking about a biologic that modulates the immune response or are we talking about a device that modulates the immune response? Because there's an immune response to everything. And I don't know -- and I'm not sitting here saying I have the answer to that, but this is exactly the type of consideration that needs to take place for all the new devices that are going to be coming on the market.

For example, you could talk about the coating of the -- was it cobalt on the polyethylene? Was that a surface coating, is that right, that you mentioned?

DR. RAO: Carbon coating of implants.

DR. BADYLAK: Oh, carbon coating, yeah, yeah. There's going to be more and more

of these types of materials that are coming, going to be presented to the FDA.

Something else, though, to consider. You know the present ISO-10? Think about the way devices are designed and eventually get to the market. You know, someone has got an idea, a particular design is decided upon, manufacturing processes are decided upon, and then one of the last things that happens is what's the immune response to this. You know, you get that far down the road from an industry standpoint, you know, and then before you even think about what if the patient has a bad response to this thing, well, already years and millions of dollars have gone into product development before you even do the first test to say that's going to elicit a particular type of response.

Then, to make it even a little bit more complicated, the type of responses are the -- you know, we put something subcutaneously and evaluate the immune response when it's going to be, you know, put in the knee. You can do an intradermal injection when you're trying to, you know, decide on hypersensitivity that -- something that's going to be an intrauterine implant. And you can just go right down the line. Yet these are the standards that have been out there forever. So perhaps a revisiting of the types of tests that have been conducted is worthwhile, dependent a lot upon clinical -- maybe totally upon clinical application.

DR. RAO: Thank you.

We had Dr. Burton?

DR. BURTON: Richard Burton. This is more to FDA. And when I look at that list, and I hear the discussions we've had both in -- some of the presenters from the audience have raised questions. My question is why, other than perhaps proprietary manufacturing patents, and things like that that might limit it, but what is the reason that the various coatings, manufacturing processes, or the actual composition of the implants is really not available to at least the doctor and certainly the patient as well?

DR. RAO: Thank you.

Dr. Taylor had a question and then Dr. Burchiel.

DR. TAYLOR: Yeah, I would agree with that. I think the critical thing is -- well, I was going to do a couple of patient examples. There are pacemakers where patients have reacted in several cases in Japan, and they've coated them with PTFE, and it resolved the problem, and in another case, they actually coated it with gold. And it resolved the problem. But I think the key is clarity with ingredient labeling. And then the issue is, with that, it becomes quantitative versus qualitative. I just had a new device orthopedic, and they were incredibly cooperative, but it's very, very difficult to find information. So a list of key contacts -- the cosmetic ingredient labeling group, CAR, used to have a cosmetic industry on-call list with people, key contacts, to get this information. That would be incredibly helpful.

DR. RAO: Thank you.

Dr. Burchiel?

DR. TAYLOR: Thanks.

DR. RAO: And then we stop at that point.

DR. BURCHIEL: So I'm looking at the guidance document from 1999, and we've seen this at every center, CBER, CDER, everybody has this. And CDRH has it as well. And the flowchart is what I'm referring to. And it talks about devices contacts to body, okay? That's the starting point. Then, yes, device contains potentially immunotoxic material, no/yes, right?

So I think that these needs to be revised when it comes to metals. I mean, I think that we're beyond the point of people saying, nah, it doesn't do that. There's a lot of literature out there, and I don't know how many -- just following up on your point a minute ago -- how many people find out too far down the road that they've got a problem,

an immunologic problem. And how they determine that and all that preclinically, that's a whole nother story. But I would say that this needs to be looked at, once again, whether that's the correct decision tree to tell somebody, you know, what is the evidence, what is the literature, what are the components? Is it likely, or do you have any evidence for or against? I mean, I think we need a little more than a yes/no thing there.

DR. FISHER: Sure. So, Dr. Burchiel, just for clarification, which flowchart are you looking at? FDA has a ton of flowcharts.

DR. BURCHIEL: I'm looking at the -- yeah, 1999 guidance document --

DR. FISHER: For?

DR. BURCHIEL: For immunotoxicology.

DR. FISHER: Got it. Thank you.

DR. BURCHIEL: And it's the decision tree right off the bat.

DR. FISHER: Excellent. Thank you.

DR. RAO: Could you turn your microphone off, please? Thank you.

Dr. Yustein, I think we're ready to try and give you a response to Question Number 3. I think the Panel generally feels that device-related factors do have an impact on the patient's response to that implant or insert. There may be multiple factors that contribute to this device-related response, including the extent of wear debris that'd generated by the alloy composition, the specific alloy composition and its predisposition to wear debris. And there are other factors that may play a role in mitigating this device-related response, including, potentially, changes in the microstructure of the implant, changes in potential coating of an implant with other substances, which may or may not introduce their own issues.

The primary thing the Panel feels fairly strongly about and fairly consistently about is that it would be beneficial to get a listing of the specific elemental composition of these

devices included on the packaging of each of these devices.

Is that adequate?

DR. YUSTEIN: Yes. Thank you. And I'll just say that we actually have started to do that in some product areas. We just recently issued a guidance document for breast implant labeling, where we are asking manufacturers to include all the "ingredients" that are contained in those products. So we've heard that from the public for other areas, too. Thank you.

DR. RAO: Thank you very much --

DR. McDIARMID: Can you add including the coatings, Dr. Rao?

DR. RAO: We did. The coating, I did talk about it.

DR. McDIARMID: Okay.

DR. RAO: We're going to skip Question Number 5 and switch to the dental amalgam things.

Let's go to Question Number 6. Question Number 6 relates to dental amalgam. Based on discussions during this meeting, please discuss the strength and validity of current science with respect to the potential adverse health impacts related to mercury exposure from dental amalgam amongst dental professionals, the general population, and subpopulations that may be more susceptible. So we'd like to discuss some of the science that you feel is incontrovertible regarding potential health impacts from mercury exposure in three different subsets of the population.

Let me start with Dr. Li.

DR. LI: In general, and in my opinion, the additional literature reviewed is very extensive, but largely confirmative to the previous knowledge and understanding of the mercury and amalgam health risks.

The risk to the professionals continue to be a concern. However, those are largely

due to the inadequacy in practicing the mercury handling hygiene. If the evidence already indicated very clearly, this recent data again added to that. If the dental professionals practice adequate dental hygiene in office, which should also have the mercury spill kit available in the office, and they have the personal protection and follow the recommendations by the American Dental Association, the overall exposure could be significantly minimized.

The real -- and, again, it's additional evidence -- the allergic reaction to the amalgam is not only to the dental professionals, but also to the general population. There are different figures about that, but it could be -- a certain number could be quite a bit. So that is another confirmed adverse effect.

Relating to the high-risk populations, including the pregnant woman, the lactating woman, as well as young kids, the new data still, again, largely confirmed the previous finding and the previous evidence. The one thing missing from this three list is the potential effect of the environmental, which eventually will have influence on the health risk. This is not limited to the spills in the dental office, but also the appropriate handling following the requirements to handle the waste of the amalgam. That's why, in general, my opinion is the evidence continued to accumulate, although it is confirmatory, but it makes the evidence stronger.

DR. RAO: Thank you.

Dr. Weisman and then Mr. Lison?

DR. WEISMAN: What impressed me from the new evidence presented, the updated view, is the epidemiology, if you will, of mercury levels in the United States, the geographic variation related to the way things are handled locally. But notwithstanding that, the importance of the mercury in the amalgam to the overall mercury burden is still high. And we're learning more about where -- whether new techniques of measuring

organic versus inorganic mercury have led us to the conclusion now that, in fact, there is some conversion from one to the other, which is not surprising because of the longevity of the mercury in the environment. And also the difficulty of actually eliminating mercury from the environment, and the kind of the pictures that we were shown about the recirculation of mercury during the lifecycle of all of us.

That coupled with the fact that very enlightened people in Europe have looked at this burden, and because the economy is -- I don't want to say better, but the economy is more efficient, or the economy may recognize the ability to treat more people with non-mercury implants in Europe, in Germany, has led to the discontinuation of this product.

And, finally, what is really compelling is the fact that there is a disproportionate accumulation of mercury in the bodies of those individuals in our society that are disadvantaged for a variety of reasons. And we've heard some interesting epidemiology of those reasons.

But it continues to be a problem in health disparities in this country, and it's something that coupled with the question that I asked initially was: Are there reasonable alternatives to amalgam fillings in the United States? And, obviously, there's back and forth here, but clearly there are. And that the non-amalgam implants and fillings is a matter of education, which I support, and novelty and innovation, which I certainly support, and the growth of modern dentistry techniques, which I support.

So given all that, my feeling is that mercury-containing amalgam should probably be on its way out. Now, how to deal with that as far as the FDA is concerned, what kind of roles and restrictions to do I think should be probably a matter of discussion. Should it be related to certain populations? Should it be related to education? Whatever it is, whatever the mechanism is, it'll be some kind of uniquely American, you know, mechanism of doing things, unlike what might happen in Germany, where they said no more, no mas,

okay? But whatever it is, I think it's something that should be done.

DR. RAO: Thank you, Dr. Weisman.

Mr. Lison?

MR. LISON: I agree with the last commentator. I think I have seen no evidence that the other potential options present any personal harm to anyone. I think everybody would agree that mercury in the body isn't a good thing. I see no reason why it shouldn't be phased out as quickly as possible.

DR. RAO: Thank you.

UNIDENTIFIED SPEAKER: Can I respond to that?

DR. RAO: One second. Dr. Zuniga first.

DR. ZUNIGA: Thank you.

DR. RAO: And we had Dr. Li, and then Dr. Connor.

DR. ZUNIGA: Thank you. I think the scientific burden -- I agree with Dr. Li that the process that the FDA has gone through or taken us through to answer the questions has been a sequential process. I think we all agree that the science presented today and in previous meetings are strong, that the evidence that mercury exposure is dose-dependent, frequency-dependent, and dose-dependent meaning the number of amalgams per the individual.

Also, in response to the concerns that neurodevelopmental, neurologic disorders led to further exploration of subpopulations, which were done, and then the evidence suggests there's not a direct correlation. I think under the FDA's regulations, this now becomes, was brought up earlier, a question of informed consent. And that's not an FDA issue. That is a public and maybe a dentistry issue. And our profession needs to have that discussion with patients, informed consent, because there are other alternatives just like we seek in all surgical, medical specialties, informed consent, and it is part of the process

that brings the patient involved.

DR. RAO: Thank you.

Dr. Li and then Dr. Connor and Burton?

DR. LI: Yes. Actually, I agree with you. For amalgam, the exit direction hasn't -- did not start recently. It has been continuously in the declining. In the '50s, about 70%, 75% of private practitioners just spending their time and working on amalgams, but the recent -- the latest data I had was the turn of the century, it became probably only 5%. The dramatic increase were the aesthetic work. So there have been clear -- there has been clear trend going that way because of a variety of reasons, the safety concerns is one of them. The other aspect is the available of alternative materials.

When I was in Indiana University, Dr. Ralph Phillips was my mentor. He specifically discussed this topic with me. As a matter of fact, the availability of the amalgam at that time really served in the major purpose for the filling. There are two different aspects to consider. One is the safety of this material. If it is really risky, a high-risk, high problem with health consequences, then regardless whether we had any good alternative, we would have to eliminate it. Now, the collection of the data, including the most recent one, the white paper FDA presented to us, as I said, added a strength of our understanding.

So I think we have to consider not only the safety, but also the purpose of this material for the general population. And as a matter of fact, if we immediately ban the amalgam, then a portion of the population may not have much other options because of a variety of reasons.

DR. RAO: Thank you, Dr. Li.

Dr. Connor?

DR. CONNOR: Yeah. So I guess my struggle, Dr. Li, is when you say the general population, but the data is pointing to it's not the general population who, you know, is

tending to get amalgam these days.

So, I mean, it seems to come down to the practice of medicine, which really has three factors, right? What FDA allows you to use, what payers pay for, and what medical professionals have incentive to use, be it how much time it takes them to do it or how much money they make, you know, providing that service.

And in other countries, people have stepped up, like payers probably, and said you can't use this anymore. Payers here, because it's the government paying for, you know, disadvantaged people, don't have that incentive. The medical professionals may not have that incentive because they're trying to do as many as they can, but it sounds like once they are using other things, maybe they can do it faster, which may mean it's -- the FDA is the only one of these three inputs that has the power and maybe, you know, the incentive to intervene. Whether that's appropriate, I don't know. I'm not a dentist. Because I know there's opportunity costs to how much you can do, how many you can do.

But it seems like if a product came on the market today that said it's 50% made with a material we know is highly toxic and we're only going to use it predominantly in disadvantaged populations, we wouldn't be having a meeting, you know? FDA would not approve it without a meeting. So, I mean, I'll leave that right there in terms of our discussion, but if this were coming on the market today saying it's 50% highly toxic material and we're predominantly going to use it in disadvantaged populations, it wouldn't even be a question.

DR. RAO: Dr. Burton?

DR. BURTON: I think there's been some great comments, particularly Dr. Weisman, and some of the things. I have been on the previous panels with this issue going back to 2006 and have heard a lot of the same arguments. And I've seen -- particularly the data, I believe, Dr. Li, has improved over this time in terms of showing cause and effect. And if

you go back to the 2009 period, there was originally a recommendation that was toward the use -- or the change for subpopulations. And I think that what I've seen, at least personally, has been sort of a drift in these panels toward the move of getting rid of it.

The changes that have occurred in Europe -- I spend a fair amount of time in Europe and know a number of people who practice there and structural people within the government. Most of the move in Europe wasn't always particularly over just the safety issue. It was primarily an environmental issue that led to this being -- basically, it was no longer being sold because of the disposal and the other issues associated with mercury. It was not specifically because of a toxic concern with that.

But, again, I think we have started to identify that. Certainly, if there's a question of subpopulations, the reason that they came forward that we -- if there is a particular group which is at risk, we're always going to move to try to protect that group. And I think that, you know, we'll have to make a decision, the decision being if we're going to start this thing. I think it's going to disappear in this country in reasonably short order just because of environmental reasons, the same way it has in Europe and in other countries.

The only other thing I would bring forward that I think needs to be considered, then, if on the other hand you want to come out with a ban or however you want to approach that is what you do with the probably 150 million people in the United States that have existing amalgam restorations.

We do know from some of the previous studies that one of the riskiest times is the time at which it's placed and the first 24 hours of that curing. And the second point of risk is when you remove it, because it produces a great deal of vapor. And in one of the presentations showed the fact -- various devices to mitigate that for both the patient and the provider. But, again, you've got to -- is, for the existing population, the retention of amalgam considered to be safe based upon the science that's shown here? Personally, I

think that it shows that, but maybe it's time to move on to other alternative materials. Personally, they're not great at this time, but I think this gives the impetus to industry to produce something which is more acceptable.

DR. RAO: Thank you.

Dr. Li, Dr. Suzuki, I'm going to ask you for the final comments on this.

Dr. Suzuki is one of our dentists on the Panel, so I think it's important to give his feedback. But he was also somehow involved with the ADA's Council of Scientific Research, and he is concerned that he should declare this potential conflict from the past before he makes his comments.

So, Dr. Suzuki, please go ahead.

DR. SUZUKI: Yes. More specifically, Mr. Chairman, I was the chairman of Council on Scientific Affairs of the American Dental Association, and that was the council referred to with the white papers and the official position of the American Dental Association on the safety of dental amalgams.

However, on another note, I was the dean of a major dental school, University of Pittsburgh for over a decade. I was the associate dean for graduate education at Temple University for over a decade. So I was responsible for the education and the clinical training of many restorative dentists, including those dentists that placed amalgam.

So, in particular, I guess my focus was on using currently available scientific information to choose those particular dental products for efficiency, safety, and clinically applicable situations, and so I elected during my tenure as chief education officer to continue the use of amalgams taught in restorative dentistry clinics.

Having said that, there are suitable alternatives. Glass ionomers and composites certainly are suitable. They were primarily generated -- correct me if I'm wrong -- the other dentists in the room -- primarily generated for aesthetic concerns because of the

interior part of the mouth that smiled, that's where the greatest application was. However, there's growing interest in these particular products because of the less invasive type of cavity preparations needed to place these materials, plus the dental materials themselves have really, really improved, and their longevity in the mouth doesn't approach that of amalgams, but certainly they are improving. The third alternatives are porcelain, which is out of reach of many Americans. The fourth alternative is gold, which is further out of reach of many Americans.

But I think the concern is environmental. I think the concern is for those selected population of patients that may have a "reaction" to different components of the amalgam fillings. So I think the education of clinicians, professionals, waste product removal services, amalgam traps in dental offices, needs to be further emphasized.

DR. RAO: Thank you very much, Dr. Suzuki.

Dr. Yustein, I think we're ready to provide the FDA with an answer to Question Number 6.

And I think, generally, the Panel feels in response to Question Number 6 that the evidence that was presented and is available currently confirms what was previously known and tends to move the needle a little bit further along in the direction that there is some recognition and understanding of the risks associated with mercury-containing amalgams. These risks are to the environment and also to the patient, and potentially, to the -- and to the dental professionals involved in the insertion of these.

I don't think there's been any clear understanding of a quantified increase in risk that is available currently. But the trend seems to be that when there are alternatives available to the use of mercury, the general direction should be to move away from using mercury-containing amalgams and towards non-mercury-containing products to help with dental restorations.

Is that adequate?

DR. YUSTEIN: Yeah, I'll let Mr. Adjodha say whether --

MR. ADJODHA: Yes, that is adequate. Thank you.

DR. RAO: Thank you, Mr. Adjodha.

Let's move to Question Number 7, which deals with in vivo cross-transformation of mercury species within the body and how this may impact the extent to which we know the origin of mercury species and adverse health effects attributable to inorganic mercury, or methylmercury.

Think I'll pick on, yes, Dr. Jannetto.

DR. JANNETTO: So just for the record, most testing for mercury, people are measuring total mercury. They are not doing mercury speciation. Mercury speciation can be done, but requires separate chromatography ahead of time prior to doing the ICPMS analysis.

Now, the evidence has shown that you can have demethylation and methylation of mercury, and therefore, the cross-transformation of mercury species. Historically, we have all been trained -- I was trained -- that the mercury we measure in urine, even though we're just measuring total mercury, is always elemental or inorganic mercury and that the mercury that you measure in hair and predominantly in blot is the methylated mercury form. With this new evidence that is shown, that takes that out of the water, because it could have been methylated mercury that you were exposed to that then got demethylated. And that's what we're measuring, because again, most measurements are not doing speciation.

The other point that I just want to make is that the speciation of all forms of mercury are toxic. However, the speciation does become important in the actual role of the toxicity. And for example, the absorption through the GI tract, elemental mercury

does not have very good absorption, but methylated mercury does have near complete absorption. So speciation can play a role.

And so from dental amalgams, it may be initially that elemental mercury form, it can get biotransformed, ingested, swallowed, and then be absorbed. If it is methylated in the GI tract, you can then have therefore increased potential absorption based on the speciation of that mercury in that subspace.

DR. RAO: Thank you.

Yes, Dr. Li?

DR. LI: Yeah, thank you very much of that. I totally agree with you. For a long time, there had been assumptions or hypotheses that there are such a conversion. I'm very pleased to see the initial data, and I think this should be encouraged because this will help to further improve the quantitation of the different species of the mercury, which would be very helpful to understand the toxicological part of the different species of the mercury especially for those associated with the amalgam.

DR. RAO: Thank you, Dr. Li.

Any toxicologists with any thoughts?

Dr. Weisman?

DR. WEISMAN: Asking a question. Is it only within the human body where this cross-transformation takes place or does it take place in the environment? Or does it take place in fish? You know, in other words, it is only the human part of the cycle of mercury, because we create this amalgam and put it in people, where the cross-transformation issue takes place?

DR. RAO: I don't think we know for sure, but we did see some evidence to suggest that there are bacteria that will convert the inorganic mercury to organic mercury in the flora, you know, in the ocean. So we did see some evidence to that effect that there are

some -- there is some bacterial conversion. Now, beyond bacteria and humans, I don't know that we heard any additional evidence.

DR. WEISMAN: It sounds like that we're the major player in the conversion story. Is that --

DR. RAO: Or we're the major player that's been identified to this point, you know? I don't -- I was going to ask that question whether they've actually tested this conversion in fish, but I just don't know if they have an answer for whether fish can convert -- actually, they are converting inorganic to organic, but can -- yeah --

DR. McDIARMID: Right. Minamata is eating the fish, and that was organic mercury.

DR. RAO: Yeah, that's organic, yeah. But are there -- I don't have an answer to your question as to whether there are other animals or other chemical processes or other systems that convert one to the other.

Do we have someone from the FDA that can provide? Yeah, please, please.

DR. GOERING: My name is Peter Goering. I'm a toxicologist at the Center for Devices. Mercury species cross-transformation takes place in the environment, as our speaker, Dr. Franzblau, explained to us yesterday in the diagram. There is a lot of mercury waste that's inorganic that gets settled into the sediments and water where bacteria can biotransform it to methylmercury. That's where the major exposure to methylmercury in fish takes place. So environmental transformation, chemical transformation, is quite a significant process in changing mercury species and is responsible primarily for the methylmercury contamination of fish and magnification up the food chain to humans.

DR. RAO: Thank you.

DR. GOERING: I also think Dr. Franzblau talked about methylation and demethylation. He was more convinced that there is demethylation of methylmercury in humans, but I think his view was that methylation of inorganic was much, much less a

contributor in that pathway.

DR. RAO: Thank you.

DR. GOERING: Yup.

DR. RAO: Dr. Yustein, I think the Panel generally feels that there has been some increased knowledge of the process of conversion between the methylated and non-methylated forms of mercury and that there is more transformation from one to the other, both within humans and in the environment, and in other species. One of the issues is the current testing for mercury has been largely based on -- doesn't clearly speciate between the different types of mercury, and that results in a knowledge gap, where we don't have enough information to answer specific questions as to the toxicity of one versus the other or the relative contents of one versus the other within humans or in the environment.

Is that adequate?

DR. YUSTEIN: Yes. Thank you, Dr. Rao.

DR. RAO: Thank you. Let's go on to Question Number 8. Question Number 8 deals with gaps or challenges not addressed in the FDA's Report on Dental Amalgam and what we would recommend in order to help narrow these gaps. And I'll go around the room and see if anyone has any thoughts on this.

Dr. Dykewicz?

DR. DYKEWICZ: I think there's uncertainty about the additive effects of mercury neurotoxicity and other heavy metals, such as lead. I'm speaking as someone who grew up in Flint, Michigan before a time when lead was in the water, but the reality is that there are people, often underprivileged, who are in environments where they're getting exposure to lead, plus mercury together, and we don't have a good real handle on what the neurologic downsides of that would be, which also I will say out of order, I mean, I

think it's unconscionable that Medicaid children in some states are forced to get amalgam and not be able to be offered alternatives in an informed consent with their parents. So I think we need more studies, but do we wait to see that there's neurocognitive problems before we take some action? And my thought would be consistent with Health Canada, for instance. We should be saying that other non-amalgam fillings should be used or at least considered in children.

DR. RAO: Thank you.

Dr. Weisman and then Dr. McDiarmid?

DR. WEISMAN: Specific question is a good one, because the risks of the amalgam in the susceptible populations as well as the risks for removal of the amalgam, which we've heard might even be greater to that particular population, and is that population vulnerable, and which population is vulnerable to the risks for removal as to also the risks for the implantation of it to begin with. So I think there's evidence, but we need the FDA to recognize the challenge of addressing this evidence and how to put it out in the public so that one doesn't necessarily create a scare, but one creates the proper environment for really understanding how to deal with this kind of evidence. And so the steps that are taken in a public health process should be adhered to.

In addition, with the new information that's out there, this could be a challenge to researchers, for example, to -- or to the NIH to set up some RFPs or RFAs to be able to address some of these questions. You know, there's a whole world out there called implementation science, and that would be the world where the question about what to do with the issue of addition or removal of the amalgam should be addressed in an implantation science research project, which I would fully support.

So I think this Question Number 8 is probably the most important question of all the ones being asked about it, and I think the FDA should pay special attention to the

comments from the Panel and try and address it.

DR. RAO: Dr. Taylor?

DR. McDIARMID: I was next.

DR. TAYLOR: Just to follow up on that --

DR. RAO: Sorry about that, Dr. Taylor.

DR. TAYLOR: Go ahead.

DR. RAO: Let me just hold off.

Dr. McDiarmid, yes?

DR. McDIARMID: Thank you, Dr. Taylor. I would like to focus on the last part of that question and say vis-à-vis what do you say or communicate about susceptible populations, and I'm a little bit concerned that what we ended up saying, because we don't have really enough time, in Number 6 doesn't get lost here.

But I think here's what we do know. We can see a dose response in terms of mercury concentrations as a function of the dose being amalgams. We know that children and their developing brain are particularly susceptible to neurotoxicants. I'm a little uncomfortable because people don't think the science is quite a homerun to say that susceptible populations, such as children, it's not quite -- the evidence isn't quite there for us to say maybe we shouldn't be using amalgams in children, pregnant women or breastfeeding women. But we also know the behaviors of metals from pregnant moms and in breastfeeding women.

So I kind of have to say surely there could be a risk message that the FDA could take a position that we're not talking about digging amalgams out of people's mouths, but we need to stop planting them in the particularly vulnerable populations. And I think you can have a risk message that says out of an abundance of caution, we must take these steps, as the evidence accrues. But I really think that we have all of the pieces except for these

outcome messages that people seem to want to -- I mean the outcomes in epi studies, for example, that people want to have a brighter line.

But I think between that and the conflict of interest that we're kind of in because the payers are hiding behind FDA to fail to pay for a potentially more expensive intervention, especially in people who need this type of assistance, people who already are exposed to other neurotoxicants because of where they're living, as Dr. Dykewicz said, I really would hope that at least this makes it into the record that -- I'll speak for myself and say I think that the evidence is there because we can show an exposure and we know the behavior of these neurotoxicants in the developing brain of children. We really need to think about continuing to just bless this because the evidence isn't quite there.

DR. RAO: Thank you, Dr. McDiarmid.

Dr. Badylak?

DR. BADYLAK: Yeah. So I've learned more about mercury in the past 2 days than I did up until 2 days ago. So I'm coming at it from a standpoint maybe an objective standpoint of how decision are made on whether a device is safe or not. We know mercury is toxic. We know copper is toxic. We know cobalt is toxic. We know silver is toxic. Those are all in medical devices. It's a matter of where our gap in understanding is in the metabolism, the pathophysiology of mercury in the body. So that's, to me, where the resources ought to be devoted to understanding what's happening with this device when it's put in the body.

I'm a little bit uncomfortable with recommending that something be removed from the market -- and this is -- I'm divorcing now medical issues -- this is a separate point -- I'm a little bit uncomfortable with removing a device without the typical scientific evidence that we depend upon for everything else that -- to say something is, you know, black or white. And if we don't have -- I mean, I would bet that if the incentive for the new

products, the ceramics and the composites, and such, to produce a device that is less expensive than amalgam, this wouldn't even be a discussion. Nobody would use amalgam anymore.

But if you take it off the market, now, where is the incentive to make more -- make devices that are more economically viable? I'm not quite sure how you can also take something off the market for a particular population and leave it for others. I understand the rationale for that, but boy, that would really, that would really be tough to do, I think.

I think this 20 years of saying we don't have enough information, it's not definitive one way or another, that can be solved if we would just focus on it. I think back to the mid-'90s, when silicone breast implants were taken off the market because there was a potential concern without evidence. So for 5 or 6 years, this device was not available to women. And after the focus on it, we realized there wasn't -- it wasn't toxic. Now they're back on, and women have more choices this way. Maybe this should be treated the same way, you know? I'm not saying that's the right answer. Just I wanted my two cents on the record as well.

DR. RAO: Thank you, Dr. Badylak.

Mr. O'Brien?

MR. O'BRIEN: I support the move that we said in terms of moving the trend away. I would only caution -- and I think we do have to say something very positive to those populations that we know are vulnerable and risk. I think we have a very recent example with the opioids, and the CDC guidelines that went out that had all good intentions, but it resulted in a catastrophe for patients in the field.

And so I think that it really does need -- if there's going to be information conveyed, it needs a cross-agency, very clear instruction with professionals and the patients to understand because everybody is going to want to take them out now, and that's going to

create its own problem, etc. So it becomes -- it is incredibly important to really think out a very comprehensive plan along that trend to remove and start to fend away from amalgams.

But my wife has amalgams, and I'm going to go home right now and make sure -- and the reason she can't take it out, the dentist said because of the amount in there, they can't support -- the current technology cannot support it, so it would have to be whole replacements, so --

DR. RAO: I've been feeling some tremors come on in the last 2 days myself.

(Laughter.)

DR. RAO: Well, Dr. Yustein, I think the Panel generally feels that there are risks -- there are gaps that exist with regards to dental amalgam primarily related to a lack of communication to the population at large whether by the dentists or by the FDA, or by our society at large as to the risks, the potential risks of mercury-containing amalgams, and potentially, more specifically, in vulnerable subgroups like children.

The other significant gap is that the risks of removal of these amalgams are not entirely known at this time, and that deserves more study and research by the FDA or other federal bodies.

Is that adequate, Dr. Fisher?

DR. FISHER: Yes.

MR. ADJODHA: Sorry. Can I ask a question?

UNIDENTIFIED SPEAKER: Yeah.

MR. ADJODHA: So the last part -- this is Michael Adjodha, the last part of the question asked the Panel if FDA should convey information to the public, what is known or unknown. Is there a recommendation on that?

DR. RAO: I think -- I'm not sure that the Panel has clear information that is clearly

known about the risks of this that needs to be conveyed in an abrupt fashion. But I think certainly, over time, as the evidence comes out, as additional evidence comes out, we need to make sure that this is adequately conveyed to the population at large and maybe subgroups within the population.

At this time, I think, like Dr. Li suggested, the evidence is confirmatory to what's existing to this point, and perhaps likely incremental, but not necessarily in any huge amount in a greater fashion.

I'll let Dr. Weisman add to that.

DR. WEISMAN: Well, I think the lifecycle of mercury in our population, the information that's come out in the last few years is really interesting and potentially very useful for our understanding of a number of issues, including amalgam implants. But also, there's issues involving waste disposal and lifecycle and conversion. You know, all that information really, I think, that's not dangerous information. That's not going to make everybody run to get their teeth pulled. I mean, this is very important information, but -- and it adds to the body of knowledge about the next steps individuals should take. People that run these plants and do waste, and you know, all that is, you know, there's an audience for that as well.

So I think that the evidence gap is there about the lifecycle of mercury, and I think the FDA is not the only agency that's supportive, but should put the power of their voice behind getting that information out there.

DR. RAO: Maybe just thinking aloud, although this hasn't come up in the Panel at large, the FDA announcements for fish and for mercury levels in fish could be revisited to make that a more comprehensive announcement of the overall potential effects from mercury from fish, from dental amalgams, and from the environment at large. That could be something to look into.

Dr. Taylor?

DR. TAYLOR: Well, just to follow up on that, I would associate myself with those remarks and with Dr. McDiarmid. I mean, I think it was suggested that NIH be involved, National Institute of Child Health and Human Development, in terms of looking at gaps. The other thing that was overwhelming, again, as Dr. Li and others have pointed out, is the occupational part of it. I don't know one agency of the government recommending to what the others -- how that works, but certainly, NIOSH clearly should be involved with this if they haven't, and perhaps even OSHA from the occupational standpoint at least as far as education, and as Dr. Weisman said, NIH and National Institute of Dental Health, so thanks.

DR. RAO: Thank you.

Let's go to Question Number 9. So now let's go back a little bit, think not just about dental amalgam, but also about metals in general, so metals and dental amalgam, metal implants, stents, gynecological issues, hip and knee replacement implants, other replacement. So what are the areas of scientific uncertainty and sources of new evidence or research/innovation needed to enhance our ability to understand this?

Dr. Christian and then Dr. Jacobs?

DR. CHRISTIAN: Thank you. Yes, I wanted to focus on the word "mitigate" and come back to our conclusion about Question Number 3. And this was something that was brought up by the public, and I wanted to make this clear, that industry supports the right to know what materials are in devices. And industry is willing to work with the FDA in providing that information. And we believe that providing that material information will assist the healthcare providers in making the most appropriate decisions for their patients, which could lead to the mitigation of these reactions occurring.

Thank you.

DR. RAO: Dr. Jacobs?

DR. JACOBS: So I'd like to propose a few ideas for additional research and innovation to enhance our ability to understand this area. We talked about National Joint Replacement Registries as powerful tools. And I want to expand on that and talk about National Implant Retrieval Registries. This is not a new idea. This has come up before at other FDA venues. It still does not exist. We learn a tremendous amount from retrieved implants. If we also have accompanying tissue and blood specimens, we can do omic studies, histopathology. I think that's a resource that I encourage us to develop so that we can leverage it to get some really basic answers.

Second thing I'd like to propose is more robust preclinical testing modalities for tribocorrosion processes. We heard our corrosion speaker talk about existing standards in ISO and ASTM. And I think that one of the things we've learned in orthopedics is that while static corrosion tests can be helpful, really the dynamic corrosion tests, where you have combined, electrochemical and mechanical issues will give you much more insight on the performance of, for example, metal-on-metal bearings, but even metal-on-metal modular connections. I think that that would assist us in perhaps screening better materials and designs that are less susceptible to tribocorrosion mechanisms.

One other area that really hasn't come up yet but I think is relevant for the discussion of corrosion is that there's also a new understanding that inflammatory cells themselves can be players in accelerating corrosion in certain circumstances, Jeremy Gilbert, Dar Lab, others have shown that there are cells in corrosion pits, and it's certainly plausible and feasible that the cells themselves are participating in the degradation process, and that's something I think we need to further understand is there may be some targets and, you know, therapeutic targets in that region that can perhaps modify cell response. Those are three suggestions.

DR. RAO: Thank you, Dr. Jacobs.

Dr. Lemons?

DR. LEMONS: Strong support for the comments made by Dr. Jacobs. And I simply point out as a participant in several standards organizations, dental and medical, we have documents in progress on the topics you've raised, Josh, and I think what's important is we need help to expand in the biocompatibility area significantly from where we are now, related to the questions today. But we really need more participation, individuals with expertises in the general interest and the clinical. We're fairly well represented in the industry, but however, we need more individuals with expertise. And the limitation here, in general, is funding for those type individuals to -- for travel. So, therefore, we need, I think, to recommend as much as possible that we have participation in these things because consensus really needs to be carried to the industry with regard to the products that are made available.

DR. RAO: Thank you.

Dr. Weisman?

DR. WEISMAN: I'm not sure that a registry as currently defined would be feasible. I think a cohort of at-risk patients with some specific data collections that we would think today that would be state-of-the-art, cell lines, lymphocytes that are alive, the ability to do some sophisticated immunologic work, all salted away in a freezer in a specific cohort, where certain questions need to be answered, with the smallest number of patients possible and the largest attempt to, you know, collect them; that, to me, would be a really worthwhile way of spending some money because we don't know what the technology would be, what the technology would be 3 years or 5 years from now, but we would have those samples.

A registry itself is just a nonspecific collection of the kitchen sink and then just

waiting for things to occur down the line. May not be the best approach. I think the cohort effect, refining it more specifically with collection of biologic materials and the appropriate follow-ups so that every single patient that comes in to get a joint replacement is followed and not just the ones that return back to the orthopedist's office for follow-up. Because that's one of the biggest problems all along with these kinds of registries or cohorts, is lost to follow up of the most important ones, which are the ones that don't come back to the office.

And make the data collection independent of whatever bias the orthopedic surgeon has one way or another. That is, you'd be using people outside the profession to contact these patients and gather some of the clinical information that would be standardized and appropriate for the questions that we need to be answered. So I think that if that could be done, it may help answer some of these questions about whether or not the immune system, as you follow it along, has anything to do with the outcome of these patients. That would be the best way to approach it.

DR. JACOBS: If I can just respond briefly. The approaches are not mutually exclusive, obviously. Both implant retrieval registry and the cohort you suggest I think are both areas where we can really leverage a lot of information.

Implant retrieval programs already exist in multiple centers. I know Jack Lemons had one for years in UAB and we had one at Rush, and there's others throughout the country. It's hard to fund them. They're hard to support. And yet we get tremendous information from them. So a more national approach to this fostering collaboration amongst various implant retrieval labs I think is really going to enhance our understanding of the performance of devices and the patients' response to them.

DR. WEISMAN: I'm not arguing against that. I'm arguing for it. In addition to that, a cohort effect, where you start at the very beginning.

DR. JACOBS: Agreed.

DR. RAO: Dr. Germolec?

DR. GERMOLEC: So this is not necessarily an area of scientific uncertainty, but I really think we need to develop a much better communication strategy overall from the outset of labeling to collecting information from patients pre- and post-marketing.

One of the things -- I will say the word multifactorial again. And one of the things that I've come away from this discussion today is that there are so many factors that contribute to implant success or failure, and there are things that are not considered.

I think about a patient that comes in. They're in pain. They want an implant because they're in pain. They're likely taking NSAIDs, which we've heard affect the success of implantation. They're in pain. Again, they may be depressed because they're in pain, and they're taking antidepressants.

It is a whole package, and we need to assess the whole package at multiple points in order to understand what the scientific evidence is underlying the factors that make implants successful or not.

DR. RAO: Thank you.

Dr. Connor?

DR. CONNOR: Yeah, I think like Dr. Christian, I think that mitigate is probably the key word here. From, you know, the statistician's perspective, I fully understand that it's ideal to predict who may have, you know, an adverse health outcome here, but I think we're a long, long way from being able to do that well. In Sid Mukherjee's book on cancer, he talks about how, you know, Kennedy said we're going to go to the moon by the end of the decade in 1961, and we did. But it's because we understood Newtonian physics. When Nixon declared war on cancer, we didn't have the slightest idea about, you know, biochemistry and cellular genetics and all these things, which is why, 45 years later, we're

a long way from that.

And the idea being there is, you know, we talk about gender, and we talk about autoimmune, but it's really something more complicated that we probably haven't even begun to understand yet. And even the questions here talked about devices and patients separately, but it's clearly the interaction of those two things.

So we are so far from being able to predict who's going to have an adverse event, and certainly doing that well. So I think mitigating is the key. I hate to say that we need to accept some of these terrible adverse health outcomes are going to happen, but from a public health perspective, I think understanding how to identify those as rapidly as possible and then what to do in those patients is the most patient-centric thing that we can do, and that should be the focus in terms of most efficiently allocating our resources.

DR. RAO: Thank you.

DR. WEISMAN: Can I ask him a question? Are you referring to the outcome of the joint replacement as the outcome variable or, you know, the whole satisfaction, everything, or are you referring to the presence of unwanted effects, toxic effects, or specific effects that can be measured, you know, they have tools, along the line? Which are the areas --

DR. CONNOR: Yeah, I think the latter, and that's a big picture, right, whether it's, you know, an allergy response, an immune response. And it's hard to quantify what that is, and I fully appreciate how difficult that is. But I'm just saying that I think trying to predict who will have adverse health outcomes, and that's a big umbrella, is nearly impossible with the current scientific research tools, and the best allocation of our resources is when those happen, trying to figure out how to help those patients as best and as rapidly as we can.

DR. WEISMAN: I was arguing a primary prevention strategy rather than a secondary

prevention. That was the argument I'm making. And maybe for the statistician, you'd think it'd be too difficult to do a primary prevention issue because of the large number of people and the small number of events? Is that what you're --

DR. CONNOR: That's exactly right. And I think -- I hate saying anything is impossible, but given the current tools -- and really what is probably happening is, you know, like I said, is not gender-related, even though it's more common in women, you know. It was more common in patients with endometriosis. It may be more common in patients with autoimmune family of diseases. But what is really causing it in an individual patient is probably at a level that we don't understand, and we're certainly not going to measure in that database. So that's why I think the best allocation of resources is when they happen, studying how can we, you know, mitigate that and fix it as soon as we can.

I totally agree what you're suggesting is ideal. I think it's going to be a lot of money and a lot of resources that isn't going to help patients.

DR. RAO: Thank you.

Dr. Badylak and then Dr. Pollard?

DR. BADYLAK: Two quick comments. One is listening to a woman this morning talking about the impact of social media and the information and misinformation getting out there stuck with me a bit. And when I hear about patients who've had a problem because they were not informed of the potential risks, that's -- I don't want to say that's a crime, but it probably should be, you know? There has to be a better way of informing patients who have potential risk. And I think if the FDA came out and said, you know, we don't know, there's a lot we don't understand about this, but here's the issues that the discussion is being based around with respect to mercury, you know, at least the public then knows that you're aware, you're not ignoring the issue, you're doing everything you can to take care of it, something along those lines.

Secondly is a little quicker. I would recommend that there be a re-visitation of the in vitro and in vivo testing that is conducted for really maybe all devices, but we could start with metals, because saying you do the same set of tests for metals versus synthetic materials versus degradable materials versus others, and for all different applications doesn't really make any sense anymore. So I would suggest revisiting the way we determine safety and efficacy for these types of devices.

DR. RAO: Thank you.

Dr. Pollard?

DR. POLLARD: So I would just like to suggest that, along some of those lines that were just commented on, that while all these registries are being developed and material collected and decisions made on what to do is actually to do more preclinical studies with animal models. Now, it's going to be pretty hard to put a hip joint into a mouse, because that's the most usual experimental animal that we use, but certainly, studies could be designed with probably larger animals that could be used in some of these sort of comparatives tests between different devices. But we'd certainly get a much better idea of what the early responses are in terms of -- as these materials either degrade or corrode, or whatever processes are involved and actually eliciting these immune responses, because that seems to me to be -- that early immune response seems to me to be the key to this whole process, and if we don't understand what that is, then I don't think we'll get very far.

And we know a huge amount about the -- that are involved in these things and a lot about the human and animal studies, and I think it would be very worthwhile. And the NIH would be, obviously, the place to go for that.

DR. RAO: Thank you.

Dr. Lemons?

DR. LEMONS: Decades past, there was a formation of what was called the Orthopedic Device Forum. That forum met initially up to four times a year, three, two, down maybe to one, and the three central issues raised was specific to innovation and opportunities for innovation in the world of the United States. The three issues, the initial issue that was raised was regulatory burden. And over these years, substantial progress, significant progress. The second issue was the recognition and respect to the discipline and the community at large, and I'm not sure about the progress there in recent years. But the third issue, which continues today, which I think is a part of the equation in gaining scientific information was litigation. And the situation in litigation in the United States compared to the world, and the amount of information that is specific to the litigation does not come into the public domain, where that needs to be in the public domain to make progress and conduct the appropriate scientific investigations to answer key questions.

DR. RAO: Thank you, Dr. Lemons.

I think we're ready to take a shot at this, Dr. Yustein. I think the Panel generally feels that we need additional information on metal-containing devices, implants, dental amalgam, and metal in the body at large. It's unclear exactly what the best way to go about this may be. Registries and/or longitudinal cohorts of some type may be helpful. But on the flipside, the statistical rarity of these incidents also create another opportunity where we may be able to get more information by studying isolated incidents where there has been failure or some type of response rather than studying the population at large. So there's two approaches, either identifying the problem areas and attacking them with more intensity or studying the population at large.

Retrieval studies, tissue and blood testing in patients who have had failures or immune responses to some degree may be another area for focus and study. The Panel is

happy to say that industry in general and the Panel in general supports declaration of the composition of all these metal devices. And it appears that industry supports this stance as well.

I think the Panel generally feels that we need improved preclinical testing of devices that are to be placed in the body. And specifically, in terms of corrosion testing, we've got to move beyond just mechanical corrosion testing to electrochemical corrosion testing as well, and possibly look into the role of biological tissues in speeding up or contributing to corrosion in some way.

Overall, I think, to summarize, the Panel feels that successful outcomes of procedures where devices are implanted in the body are multifactorial in their etiology, and success depends not just on the patient, but it depends on the device, it depends on the surgeon, it depends on the technique used, and it depends on a number of mechanical properties of the device in addition to immunological or other such processes.

So I think, well, I personally am very supportive of the work that the FDA continues to do to try and move forward our knowledge in all these various aspects, and I hope that is adequate for now.

DR. YUSTEIN: Yes, I believe so. Thank you, Dr. Rao.

DR. RAO: Thank you. I think that concludes the questions we have since you've --

DR. YUSTEIN: We did skip one of the questions earlier, but I think you were starting to -- I think some of that was answered in this last session.

DR. RAO: I think we've answered a lot of that in the last session. I'd like to -- I think that concludes the question and answer session. If anyone on the Panel has any final comments they'd like to make, I'd like to open it up to the Panel so everyone feels like they've -- okay.

DR. YUSTEIN: Dr. Rao, before you read your closing statements, which I assume

you're about to do --

DR. RAO: I think that was kind of my closing statement.

DR. YUSTEIN: Okay. Well, so before you do, on behalf of the Food and Drug Administration, I would like to thank the Panel. I think we had all the right expertise here. And the participation and the discussion was extraordinary. I wish we had an extra day to continue our discussions. I think that you guys all brought up excellent points. We took a lot of notes. We will also wait for the transcript because there was a lot of information related to us today. But I really wanted to thank all of you for your time, your participation, your preparation. It's greatly appreciated, and to the members of the public as well. We appreciate everybody's attendance and participation. It does mean a lot. And we are listening. So thank you.

And Dr. Rao, to you, especially, thank you for keeping us on time and doing such a great job. Thank you.

DR. RAO: Thank you very much.

DR. FISHER: Okay. And I'm not going to let Aron get the last word because I would also like to thank the Panel members for -- your input is invaluable. To the patients that took their time to speak and tell their stories, thank you very much, many of them at their own expense. I want them to know that your voice was heard. Thank you very much.

And Dr. Rao, like Dr. Yustein said, you're a great Panel Chair. Thank you very much. You kept us on time and on task, and you did a great job of summarizing the Panel's comments, so thank you very much.

DR. RAO: Thank you very much. And I'm not going to let you have the last word either.

(Laughter.)

DR. RAO: Thank you very much to all of our distinguished Panel members. I think

all of us, all of you, did a great job in advancing patient care and patient safety and came to the Panel well prepared. It was a lot of fun working with all of you. So thank you very much.

And thank you to Ms. Asefa for coordinating all of this.

The November 14th session of the Immunology Device Panel of the Medical Devices Advisory Committee is now adjourned. Have a wonderful evening, safe travels to all of you, and goodnight.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

IMMUNOLOGY DEVICES PANEL

November 14, 2019

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter