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FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES RADIOLOGICAL HEALTH

ORTHOPEDIC AND REHABILITATION DEVICES PANEL
OF THE MEDICAL DEVICES ADVISORY COMMITTEE

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P R O C E E D I N G S

Introductory Remarks

MS. NASHMAN: Good morning. My name is Jodi Nashman. I am the Executive Secretary of this panel and a reviewer in the Orthopedic Devices Branch.

I would like to remind everybody that you are requested to sign in on the attendance sheets which are available at the tables by the doors. You may also pick up an agenda and information about today's meeting including how to find out about future meeting dates through the Advisory Panel phone line and how to obtain meeting minutes or transcripts.

There is also a listing of the questions that will be posed to the panel outside as well as a roster of the panel members outside. Please note that any information displayed on overheads or on slides is not directly available from me or from the Orthopedic Branch. This information can be obtained either by requesting transcripts of this meeting or by requesting this information via the Freedom of Information process. If you could pass that information along to your colleagues, also, it would be appreciated.

I am now going to read the conflict of interest statement which is required to be read into the record. It

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is noted that the deputization of temporary voting members is not required today since this portion of the meeting will not include any formal voting.

The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of impropriety. To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the Committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their, or their employer's, financial interest. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the government.

A waiver has been granted for Dr. Barbara Boyan for her interest in firms which could potentially be affected by the panel's decision. A copy of this waiver may be obtained from the Agency's Freedom of Information Office, Room 12A-15, of the Parklawn Building.

We would like to note for the record that the Agency took into consideration other matters regarding Drs. William Tomford and Seth Greenwald. Dr. Tomford reported

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that his institution has financial interest in firms at issue for matters related to today's discussion. Since Dr. Tomford has no personal interest in these matters, the Agency has determined that he may participate fully in today's discussion.

Dr. Greenwald reported interest in orthopedic firms in matters not related to issues before the panel. Since these matters are not related to the agenda of this meeting, the Agency has determined that Dr. Greenwald may participate fully in today's discussions.

Drs. Daniel Rosenthal and Joseph Lane, who are guest speakers with us today, have acknowledged professional relationships with firms whose products are under discussion today. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has financial interest, the participants should exclude themselves from such involvement and their exclusions should be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Before turning the meeting over to Dr. Hanley, I

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would like to introduce our distinguished panel members and our speakers who are generously giving their time to help the FDA on the matters being discussed today and the other FDA staff seated at this table.

For my own ease, I am going to do this in alphabetical order. Dr. Boyan, who will be sitting to Dr. Hanley's left when she arrives, is a Ph.D. in orthopedic research at the University of Texas Health Center. She is a voting member of this panel.

Dr. Daniel J. Clauw is a rheumatologist at Georgetown University and he is a consultant to this panel. Dr. Gary Friedlaender, M.D., is an orthopedic surgeon at Yale University School of Medicine. He is a consultant and guest speaker for this panel.

Dr. A. Seth Greenwald works in the area of orthopedic biomechanics at the orthopedic research laboratory at Mt. Sinai Medical Center and he serves as a consultant to this panel. Dr. Edward Hanley, M.D., an orthopedic surgeon at the Carolina Medical Center, is the Acting Chairman for this panel.

Doris Holeman, Ph.D., is a nurse at Albany State College. She is the Consumer Representative for this panel. Dr. Joseph Lane, M.D., orthopedic surgeon, works at the Hospital for Special Surgery and he serves as a guest

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speaker for this panel. Dr. Keith Markolf, Ph.D., is a biomechanist. He works in the Biomechanics Research Center, University of California at Los Angeles and is a voting member of this panel

Dr. Michael Mayor, M.D., orthopedic surgeon, is at Dartmouth's Hitchcock Medical Center and he serves as a consultant to this panel. Dr. M. Clinton Miller, Ph.D., is a biostatistician, retired professor and Chairman of the Medical University of South Carolina. He serves as consultant for this panel.

Dr. Roger M. Nelson, Ph.D., is a physical therapist and works at Thomas Jefferson University and he serves as a consultant to this panel. Dr. Leela Rangaswamy, M.D., is an orthopedic surgeon, Deputy Editor of the Journal of Bone and Joint Surgery, and she serves as a voting member on this panel.

Dr. Daniel Rosenthal, M.D., is an orthopedic radiologist at the Massachusetts General Hospital and he serves as a guest speaker at this panel. Dr. Raymond Silkaitis, Ph.D., is the V.P. of Medical and Regulatory Affairs at Gliatech and he serves as the Industry Representative for this panel.

Dr. William Tomford, M.D., is also an orthopedic surgeon at Massachusetts General Hospital and he serves as a

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consultant for this panel. Dr. Stephen Trippel, M.D., is an orthopedic surgeon at Massachusetts General Hospital and also a consultant to this panel. Dr. Michael Yaszemski, M.D., is also an orthopedic surgeon at the Mayo Clinic and he serves as a guest speaker for this panel.

DR. HANLEY: Thank you. Good morning. I am Dr. Edward Hanley. I will be serving as Chairperson for this meeting. Today, the panel will have a general discussion of study design and effectiveness endpoints for clinical trials utilizing bone void fillers.

MS. NASHMAN: Before we begin the open public hearing, I forgot to introduce the Division Director of DGRD, who would be Dr. Celia Witten, Ph.D., M.D. She is to Dr. Clauw's right. Dr. Witten will make a few remarks to frame the context of today's discussion.

DR. WITTEN: I want to thank, in advance, everyone who is here, panel, speakers and industry, for participating today. Today, we will be asking the panel for a prospective guidance for future clinical studies of bone void fillers. No vote are going to be requested of the panel. We are requesting the panel's expert clinical and scientific opinion in study design and other issues related to future efforts to study these types of products.

The search for alternatives to autologous bone

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graft has been prompted by the desire to eliminate a second surgical site and to address the issue of limited bone availability. This has led to an interesting variety of materials for use as bone void fillers.

As evidenced by reports in the literature, these devices can have a variety of biochemical and mechanical properties and can be expected to perform differently from one another.

To date, there are two devices approved under PMA and one cleared for marketing under the 510(k) regulation. The panel has been provided general background information regarding these devices in their packet. The FDA is seeking panel input on issues related to mechanical properties and preclinical testing of bone void filler materials.

These requirements may vary depending on the material characteristics such as resorption rate. Other variables, such as anatomical site and associative mechanical loading. The type of bone fracture defect size may also be important.

Panel input is being sought on what the important mechanical properties for bone void fillers are taking into account these material and clinical differences. Panel input regarding clinical-study design is being requested. We are interested in panel recommendations regarding

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considerations that would affect study design in assessing the use of this device in different anatomical sites and indications.

We are interested in panel recommendation regarding the radiographic criteria that are most meaningful for evaluating device effectiveness and to what degree radiographic data can be expected to correlate with clinical outcome. We also would like your input regarding clinical endpoints and assessment tools that would be most appropriate.

We have invited several guest speakers to make presentations related to this discussion and will be presenting specific questions to the panel for discussion afterwards.

Once again, I would like to thank in advance everyone who is here, the panel speakers and industry for participating in the discussion.

Thank you.

DR. HANLEY: Thank you.

Open Public Hearing

We will now proceed with the open public hearing session of this meeting. I would ask, at this time, that all persons addressing the panel come forward and speak clearly into the microphone as the transcriptionist is

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dependent upon this means for providing an accurate record of the meeting.

We are requesting that all persons making statements during the open public hearing of the meeting disclose whether they have financial interest in any medical device company. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any.

Is there anyone who wishes to address the panel? Please come forward.

MR. BALDING: My name is Dave Balding. I would like to say good morning to the members of the panel, representatives of the FDA, ladies and gentlemen.

[Slide.]

I am Director of Quality Assurance and Regulatory Affairs at Interpore International. I am a shareholder and I do have a financial interest in the company.

[Slide.]

Consistent with the subject matter of today's panel discussion, I would like to briefly familiarize you with the clinical information on the Pro Osteon 500 Coralline Hydroxyapatite Bone Void Filler.

[Slide.]

Pro Osteon is one of two bone void fillers on the

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market today. These two bone void filler products have undergone clinical IDE evaluation and received FDA approval as bone void fillers for certain orthopedic indication through the premarket approval process.

[Slide.]

For those of you who may not be familiar with Pro Osteon, the product is derived from the exoskeleton of marine coral which is a pure form of calcium carbonate. The calcium carbonate is converted hydrothermally to crystalline hydroxyapatite.

The result product maintains the original trabecular structure of the coral which is similar to human cancellous bone, as shown in this slide. When Pro Osteon Implant 500 is implanted in direct apposition to viable bone, the implant becomes vascularized and is ultimately incorporated with new bone through the body's natural remodeling process.

[Slide.]

Clinical testing of Pro Osteon commenced in 1982 at nine institutions. 166 long-bone defects in 159 patients were enrolled from June, 1982 to February, 1987 in the study for repair of metaphyseal and diaphyseal defects. The patient population comprised 134 acute fracture defects, 24 delayed union/non-union, repairs and eight cyst/tumor

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defects. 119 defects were in the metaphysis and 47 were located in the diaphysis.

[Slide.]

For the demographics, 100 males and 59 females were enrolled. The overall mean age was 37.4 years.

[Slide.]

The most frequent site of implantation was the tibia, followed by the femur and, following that, the radius, ulna, humerus and fibula which accounted for balance. Comminuted fractures were the most common type of fracture repaired followed by comminuted/compression fractures, compression fractures, segmental or oblique fractures, and there was one osteotomy.

[Slide.]

The autogenous bone-graft control population which was selected by gathering all reported clinical and radiographic data on patients receiving autogenous bone grafts for acute fracture defects and non-unions at three of the participating nine institutions during the years of the Pro Osteon study.

I might add that the control patients were concurrent but not prospectively randomized in this study.

[Slide.]

Clinical healing was defined as full

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weight-bearing or functional use of the extremity with no more than mild pain. Radiographic healing was new bone growth obscuring the fracture line.

The data were analyzed for mean time to clinical and radiographic healing. Pro Osteon patients had equivalent or shorter mean time to healing when compared to the autographic control group using a general linear model approach for analysis of variance for mean time to healing.

[Slide.]

Hardware was removed in 44 Pro Osteon patients with an average of 21.0 months post implantation. The average follow up, post hardware removal, was 51.4 months. To date, there have been no instances of complications or refracture following hardware removal.

[Slide.]

In addition to the analysis of human patterns, biopsies were done at the time of hardware removal for evidence for the progression of healing. 34 of 37 biopsies demonstrated bone ingrowth. 18 of these biopsies, all of which had bone ingrowth, showed the mean volume of bone to be 36.1 percent while soft tissue was 33.4 and implant was 30.7 percent.

[Slide.]

Complications reported in this study were similar

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to complications encountered in patients who had autogenous bone graft. 37 of 159 Pro Osteon patients experienced complications. None of the complications were attributed to the Pro Osteon by the investigators. The most frequently reported complications for both Pro Osteon and autograft controls were infection, loss of reduction, malunion and delayed union/non union.

The IDE was officially closed on December 17, 1992.

[Slide.]

I have shared the described study in hopes of offering you some insight which may be of assistance in your further discussions today. Interpore respectfully requests that during your deliberations today that the following specific recommendations be considered and discussed.

One, we would suggest that bone void filler should have IDE clinical evaluation prior to approval for marketing. Second, prospective, randomized autograft controls should be used where controls are used in studies. The use of allograft is not recommended.

Third, we would encourage the use of autogenous bone with bone void fillers in large defects. This is because bone void fillers are, by the definition of bone void fillers, osteoconductive and not necessarily

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osteoinductive. Therefore, the use of autogenous bone as an augmentation material, particularly in large defects, should be endorsed and recommended.

The addition of autogenous bone with a synthetic graft material will immediately bring the patient's own osteogenic and osteoinductive factors to the graft site.

[Slide.]

Finally, Interpore is particularly interested in the panel's comments regarding the following issues. One is the consequences of premature bone void filler resorption. The second, in doing clinical studies, looking at the ethical practice of obtaining bone biopsies.

Other issues to be considered are whether bone void fillers should be approved by the site indication or simply by the type of bone they are intended to replace; for example, where we discuss bone void filler for acute metaphyseal defects versus a cancellous bone-graft extender.

Lastly, your comments on the long-term assessment of mechanical strength endpoints; for example, issues concerning human clinical versus animal test requirements in terms of assessing mechanical strength.

In closing, I would like to thank the panel and the Food and Drug Administration for the opportunity to make this presentation. I would be happy to answer any questions

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that you might have.

[Slide.]

Finally, the last slide here discusses some prior art regarding bone void fillers and concerns with bone materials.

Thank you.

DR. HANLEY: Thank you. I was expecting Jules Verne to come up there.

Is there anyone else who wishes to address the panel?

If not, we will now proceed with the discussion and study design and efficacy endpoints for clinical trials utilizing bone void fillers. At the conclusion of these presentations, FDA will pose a number of questions to the panel for discussion concerning the issues at hand.

We have four presentations this morning. The first presenter will be Dr. Gary Friedlaender who will present an overview of bone remodeling cycle and clinical applications of issues related to bone grafts.

Dr. Friedlaender.

Open Session

Bone Void Fillers

Overview of Bone Remodeling Cycle,

Clinical Applications and Issues Related to Bone Grafts

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DR. FRIEDLAENDER: Good morning. Thank you very much, Dr. Hanley.

[Slides.]

What I would like to do in the next 20, 25 minutes is share with you the concept that bone grafts undergo a predictable sequence of events, that those events are a partnership between the graft material and the host in which they are placed, and that there are some issues about the clinical applications that influence success.

Let me begin by reminding all of us that we are talking about a very special material, a tissue that regenerates. This spectrum of regeneration includes the fact that bone maintains itself in a homeostatic sense, normally; that is, it avails itself of this regenerative capacity during fracture repair, and that these same basic principles apply as well to graft incorporation.

[Slides.]

The reason for this, the common denominator, is the remodeling cycle. It has been described in various ways but, basically, involves a circular sequence, or a continuous sequence, of events that includes inactivation process, undoubtedly with signalling, at the molecular level. This is a cellular process.

It then moves through a resorptive phase, a

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reversal of activity and then new bone formation. In an ongoing sense, this is, in fact, circular.

Just to very briefly talk about these stages, the activation events are generally attributed to a cascading sequence of very special molecules that are collectively members of the TGF-beta superfamily. I don't mean to be inclusive nor do I have the knowledge to tell you exactly how all these molecules work and in what sequence.

But there is no question that bone morphogenetic proteins play a major role in activating and maintaining this process and at least two of these molecules have been extremely well characterized and are being scrutinized for their use clinically including OP1, BMP7 and BMP2.

[Slides.]

After this molecular button is pushed, we then see the appearance of these large multinucleated giant cells on the bony surface. They attach to the preexisting matrix through a well-defined process. They have membrane pumps that allow these cells to control the environment between their cell membrane and the underlying matrix in a fashion that leads to bone resorption and a lacuna, Howship's lacunae.

There is some reason to believe that this process also leaves a signal that causes the attraction of the

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cuboidal cells or osteoblasts that then line the surface of this matrix, elaborate osteoid. That osteoid becomes mineralized engulfing some of these osteoblasts. They become osteocytes and their responsibility is, then, to maintain this very special matrix which we call bone.

[Slides.]

This is a picture of this process in its relative entirety on a single surface with an activation signal occurring causing the attraction of differentiation of an activity of osteoclasts, a reversal phase, and then new bone is made.

From our point of view, the benefit is that this causes the existence of this tissue called bone, and a tissue that is constantly undergoing homeostatic change. Important to many of our clinical applications is the amount of bone, or the mass of bone. That mass of bone can be identified and I'm sure we will talk more about how to do that later.

But that is very important in its mechanical integrity and the purposes for which we use it. This mass of bone, as you have been watching it on this slide, has not changed at all. The reason is that the mass is a reflection of the resorption activity I just described and the new bone formation activity.

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As long as those are equal and synchronous, the mass of this bone will not change, whether those processes are adding normal rate, however we choose to define that, whether they are increased as long as they are synchronous, or decreased. In fact, on this slide, they are decreased to zero and the mass of bone on this slide will never change, no matter how long we watch it.

[Slides.]

That leads to the notion that it is important to understand the mass of bone and it is equally important to understand because it affects its biologic and its mechanical properties, the speed at which this synchronous repair or, at times, dyssynchronous repair, occurs.

This can be accomplished in a number of ways, one of which is described as histomorphometry which I show here in a static phase and in a more dynamic sense. In a static phase, it is possible to quantitate the amount of the bone, to measure the length of surfaces within a specimen, to identify the thickness of those trabeculae, if you will, to identify the percent surface area that is covered by osteoid, the osteoid thickness, the percent of osteoid that is covered by osteoblasts, the number of osteoclasts, and the area of those Howship's lacunae.

A lot of information is readily available for us

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to understand and quantitate bone. In a dynamic sense, how fast bone is being turned over is also a matter that is accessible. In this case, this particular laboratory animal volunteered to have its bone formation labeled with a fluorochrome.

Over 30 days, tetracycline labeling, you can see, is obvious but not completely uniform. Over a shorter period of time, pulses of fluorochrome incorporated into the hydroxyapatite crystals can also be accomplished and measured. So we can define how many miles per hour bone is being formed.

Again, that becomes important in its biologic and its mechanical properties.

[Slides.]

Clinically, we use bone in a number of ways, as I will describe in a moment. But, during the everyday life of our patients, we treat them with a variety of modalities that influence this homeostatic process. Again, in the context of today's need to understand this context if we are going to evaluate it, I would just offer a few suggestions as to how we influence the bone remodeling system, sometimes on purpose and sometimes inadvertently.

Certainly, patients who are undergoing chemotherapy or receiving any drug that influences the

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metabolic activity of cells in general will influence those cells that we have spoken of, the osteoblasts and osteoclasts.

In this particular study, for example, it reflects, in a very qualitative fashion, animals that have received either methotrexate or adriamycin over about a four-month period of time. It is not at all a surprise that these drugs, which act in different ways and reduce the metabolic activities of these cells by different mechanisms, reduce bone formation and, in fact, reduce bone resorption.

Both the osteoclasts and osteoblasts are susceptible to these metabolic antimetabolites. In the case of adriamycin, after four months, bone volume is normal. But, as I explained, as long as these influences are synchronous, bone volume doesn't change and the naive interpretation of using bone volume alone might lead one to suspect that adriamycin had no influence upon bone as a tissue.

That would be remarkably incorrect since these activities are reduced by approximately 50 percent of their normal speed. In the case of adriamycin, its influence on osteoblast and osteoclast is negative but dyssynchronous. It is the dyssynchrony between these suppressions that results in a loss of bone volume and bone in the attacked

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skeleton in this particular laboratory circumstance is not as strong as it is normally.

Parenthetically, this bone is not as strong, under certain circumstances, even though the mass is normal. We can talk about that later during the discussion.

I just wanted to point out that there are other things on the list before we leave it that we do to people and to laboratory animals that similarly influence the way the skeleton maintains itself. Some of those things are potentially as simple as drugs such as antiinflammatory and non-steroidal drugs.

We also know electricity plays a role in the way bone is maintained.

[Slides.]

Let me move ahead through this spectrum of bone regeneration and just pay lip service, if you will, to fracture repair so we can get on to the discussion of bone grafts. But fracture repair ends in a remodeling process. It is identical, from a physiologic sense, to the mechanisms we have already discussed, or I have discussed and, hopefully, you have listened.

It begins with an injury. That injury leads to some necrosis, some inflammation, the development of a fibrovascular response, the recruitment of cells in a global

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sense. I am not trying to differentiate recruitment from proliferation and differentiation events. Often, it involves a transition through cartilage to bone that is then remodeled.

[Slides.]

This is an important set of events, but let me leave it as quickly as I described it so we can talk, really, about bone graft incorporation, per se, which, similarly, undergoes a sequence of events that you could describe with various terms but begins with an implantation, requires the participation of cells, includes two very important processes, one or the other or both, osteoconduction and osteoinduction, and then maintenance of the bone that has been repaired or remodeled.

Osteoconduction, this group knows very well. It is a passive phenomenon but an important passive phenomenon wherein a template or scaffolding effect provides a stage upon which these events occur as opposed to osteoinduction which I choose to mean this phenomenon plus the biologic signals that encourage it to happen.

[Slides.]

Critical to understanding bone graft repair is the concept of a partnership. This process will not work without this partnership intact. The graft has the

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opportunity to contribute cells. It may or may not. And they may or may not be viable cells or fully functional cells.

They tend to be a small part of the contribution of the graft. The graft clearly will provide an osteoconductive trellis or framework for these events and, under some circumstances, the biologic signals to move this process ahead in an active fashion.

The host, a critical member of this partnership, will provide all of the blood vessels, except under some very special circumstances, that eventually populate this graft material and, by and large, most, if not all, of the cells that are going to be important in homeostasis and remodeling, as well as repair.

[Slides.]

We will be perplexed throughout the rest of today and, I suspect, maybe even beyond 3 o'clock, by the fact that, as we change the prototype of graft incorporation, we change the way in which the events, in fact, occur.

So I will spend my time talking about what is traditionally called a non-vascularized graft which is a totally false concept but ingrained in our literature. By that, I mean, a graft that is not immediately anastomosed to its blood supply.

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I will talk about a fresh graft. I will spend a little bit of time talking about both cortical and cancellous tissue, autogenous in nature, and placed in a skeletal site.

If you vary any of these characteristics, you will have some impact on the way this process unfolds. The age of the recipient, we know, may have some influence. The size and the shape of the graft may have some influence on the speed of repair.

The way in which we load this graft mechanically will influence the repair process. If we pretreat in ways, that may also have some influence. We are not going to spend a lot of time on allografts and xenografts, but, clearly, the mismatch between major histocompatibility factors could also play a role if we are talking about using those types of materials.

[Slides.]

I am just trying to lay out for you the set of very complex interacting variables in this process. There are differences, in fact, between cortical and cancellous bone by their nature, by their architecture, that relate to the rate at which these tissues revascularize with cancellous tissue having a very open structure that invites revascularization far more quickly than is apparent in

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cortical bone. By most accounts, the completeness of repair in cancellous tissue is more so than it is in cortical tissues.

So, let's turn to these events in graft incorporation specifically recognizing that whether we are talking about cortical or cancellous tissues, it begins with the implantation event, the presence of a hematoma. There is some cell necrosis inevitably that leads to inflammation followed by a fibrovascular response as part of which cells are recruited.

[Slides.]

Looking first at cancellous materials, using the model described by Drs. Heipel and Herndon and pursued at Case Western Reserve where a cancellous plug of the distal femur, in this case, of a dog, was placed in a critical sized defect, if you will, a defect that would not heal in the ulna of a dog. It could be the same dog.

In this case, we are talking about an autograft. Junction of the ulna, the host site and the cancellous graft at up to one week, we will just the hematoma, the maintenance of the pre-existing cell structure, perhaps in the marrow. It is with time that we see the process of fibrovascular response emanating from the host, moving into the graft.

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There is necrosis of the marrow elements and then, over time, and this time frame is about three months in this particular case, we will see the addition of new bone formation on top of the preexisting trabecula which would be identified under higher power by the absence of cells within those lacunae.

With time, with remodeling, the amount of preexisting bone diminishes and, perhaps, could be completely removed at an endpoint.

[Slides.]

In cancellous tissue, we have a bit of a different circumstance. That fibrovascular response still is important, still occurs and still is the source of the cells that are going to be involved in the repair and remodeling. They will find their way into preexisting canals in cortical bone.

This is a Volkman's canal because it is perpendicular as opposed to a haversian system, but both are available, preexisting, acellular graft material, if you will. At the periphery of this graft, osteoclasts will appear that will begin to remove preexisting bone.

[Slides.]

As these cells work their way into the substance, these osteoclasts into the substance of the cortex, they

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will also remove bone, widening out these channels.

Here, a blood vessel has entered the cortex. Here the osteoclasts have removed some preexisting matrix. Here, osteoblasts that follow in a secondary wave, an important secondary wave, are beginning to replace the resorbed bone.

[Slides.]

In cross section, it may well look like this where you have interstitial lamellae of preexisting bone and osteones of new bone wherein a blood vessel has entered, resorption has occurred and new bone has been laid down. This process may well plateau with far less than complete replacement of the preexisting matrix.

That may be completely compatible, however, with the biologic and the mechanical functions for which we choose this graft material.

[Slides.]

This is my only side of biomechanics. What it is here to describe is the fact that this material has a certain mechanical property, no matter how we choose to define it. If the first thing you do is take away some of the bone, it loses strength. That strength does not return towards baseline until we add back to it this new bone formation.

That is a secondary event. As clinicians, we need

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to remind ourselves that this is not a mistake. This is the way the system was defined, described and will happen. We have to implant these materials and that is going to become important as I switch to my next theme.

It is important to plan for this physiologic, normal change in strength over time with the expectation that, at some point further on, it will return back towards baseline.

[Slides.]

I have described for you autogenous bone-graft repair. I have also actually described for you allogeneic bone-graft repair. There are some quantitative differences but it uses the same system of cells and the same types of events, perhaps at different rates, speeds, and completeness of repair. Nonetheless, the events are similar. For brevity, I am going to leave it at that.

Xenografts, in the past, have not had as good a clinical track record as we see with allografts and, certainly, with autografts. I believe that we are upon an era in which we can identify some of the reasons for these failures, if you will, and are rapidly approaching a position in which we can resurrect, literally, the use of xenogeneic tissues by adding back to them the things that were missing in the past.

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I also mentioned, and this is for completeness, that it is possible to circumvent some of the issues I just spoke of in terms of the time frame by immediately reanastomosing a blood supply. We only have that opportunity today, practically speaking, with autografts and we only have that opportunity where the blood supply is sufficiently discrete and the bone, itself, is sufficiently useful. That tends to be the fibula, the ribs and portions of the ileac crest as we know them today.

[Slides.]

We had a treat to early literature but I am going to go back even further. Bone grafts have been used for an enormous amount of time and I would submit successfully, as this first report indicates. "And God caused Adam to fall into a deep sleep and took from him a rib."

Over the few years intervening, we have learned to repair and replace a wide variety of clinical disorders and circumstances related to the musculoskeletal system. While it was often done empirically, and the science is not even fully caught to today, it is an enviable and proud history for us to work from and add to.

[Slides.]

Let me give you a couple of examples of what has gone on in the past and what I think will be our challenges

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today and into the future.

I am showing you a cystic defect in bone. This could be, although it isn't, a unicameral bone cyst, an aneurismal bone cyst, a surgical defect for some other reason. It happens to be fibrous dysplasia. It is a circumstance that weakens the bone.

It tends to do so in young people and it tends to be a problem because it leads to fracture. It doesn't spread. It doesn't metastasize. But it weakens the skeleton and that is perceived as a problem.

It is traditional when it weakens bone to some degree, and I apologize for using qualitative terms, but to some degree. A decision might be made to eradicate this weakness by removing the process, generally through curettage. Again, this could be a unicameral bone cyst or a benign cyst.

Then we are left with a hole and this urge to put something in it. In that context, let me mention that in unicameral bone cysts or many of these holes in bone, the literature, again, perhaps, not done as rigorously as we would like, but certainly leads to the impression that these holes in bone will repair spontaneously to a large degree and the rate at which we successfully resolve this clinical dilemma is less related to what we put in it and more

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related to how well the surgeon removes the underlying process.

I am going to get back to that theme. What I am pointing out is that the frequency at which these cystic lesions heal appears to be the same--the frequency; I am not talking about the speed--the frequency appears to be the same whether we use autograft, whether we use allograft that is frozen or freeze-dried, or whether we use, and I used to say plaster of Paris pellets because that is the way it was described in the report.

But, in fact, today, we have a variety of bone void fillers that, I suspect, will respond similarly. There is even a series where nothing was placed in these defects and the frequency at which they repaired is the same. The speed varies. It is because it is my job to complete remove this process, not how well I pack it or with what I pack it.

For many years, I used to be called and asked how tightly to pack the bone graft material in these defects because it recurred. When you see a little area that fails to have bone graft in it immediately after the procedure, it is not because you have failed to pack these crumbs of important material in the extense of the lesion, it is because you left something behind and it prevented it from being filled with the bone graft material.

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So it is unfair to blame the bone graft for all of the recurrences that we see in this clinical circumstance. That is my point.

[Slides.]

Just to make the dilemma even more crystal clear, or less crystal clear, depending on your point of view, this is a fracture that was closed that failed to heal. That happens. This is a fracture that was then plated with 1970's metal and some autograft and it failed to heal. That happens.

This is a fracture that was then plated with autograft plates of cortex and it failed to heal. And that happens. I had the luxury of sitting in the Navy's tissue bank when a request came in for some cortical plates of allograft which I supplied. That was my job. This healed. And that happens.

Why? I couldn't give you a clue. Perhaps it was time, and I am not saying that this fracture would only heal with allograft freeze-dried plates from the Navy tissue bank. It was interesting to me because, as a budding scientist, I knew the tissue type of this graft and of the patient and this was one of 20 percent of the patients in this series of 50 that became sensitized to the HLA antigens of the donor graft and, like the other six, went on to a

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successful clinical resolution of the problem for which the graft was used.

[Slides.]

Motorcycle rider, segmental defect. We would treat this in a number of ways today and not have a consensus about the best, I suspect. In the mid-70's, one of the more popular ways was to take a segment of allograft for this particular circumstance.

I think you can see that we are asking this segment of bone graft to do something different than fill a cystic defect. That, again, I think is a theme we will come back to. It had to be chosen and implanted in a way, and I would implant it differently today and fix it differently today--but those considerations have to be taken into account in this specific clinical situation--

[Slides.]

--as in this. I think I am getting to the end of my clinical review here. This is an aggressive tumor. It happens to be an aggressive giant-cell tumor. It could be any of a variety of other aggressive lesions that the surgeon decided required its total removal.

Over the last 20 to 25 years, we have been treated to the opportunity to be able to resect these lesions with the advent of superb chemotherapy and superb imaging

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techniques that allow us to be more specific about what we remove.

Here, it has to be reconstructed. It can be reconstructed in a variety of ways including metal and plastic and including here a biologic replacement which is an allograft. This is one of the reasonable ways in which we can proceed.

[Slides.]

Again, we can talk about the characteristics of that graft and what is important to its clinical success. Let me remind you that it is a partnership between the host and the graft. The host will provide all of the blood vessels and most, if not all, of the cells. The graft will provide the trellis and, in many circumstances, may have an opportunity to actively signal the ingrowth of these vessels and cells.

This also means that, as clinicians and as scientists, we have several areas in which we can fail as well as succeed based upon host and graft factors. Let me outline for you, especially, the local host factors which interfere with clinical success in the hopes that this will be useful as we design our ongoing clinical studies.

[Slides.]

My favorite local factor is

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polymethylmethacrylate. As I have said for the last 20 years, now matter how hard I pray and in what language, I have never seen polymethylmethacrylate heal. If you put it between the surfaces, or between two portions of the skeleton that you want to heal, it will not happen.

We have to remember, as marvelous as this material is, it does not repair. You have to define what it does and use it for what it does. If you put in between the ends of two bones that were fractured or resected, it is unlikely to heal. In this case, the lesion that was resected and replaced with polymethylmethacrylate and for which a rod was introduced went on with slow fatigue to fail.

[Slides.]

Unfortunately, this person got angry at the person that made the rob. That, I think, was inappropriate and it is not the fault of this material. The rod did what it was supposed to do and the polymethylmethacrylate did what it was supposed to do. But it was an inappropriate combination for this particular goal of union of the bone.

We know that infection is not an absolute contraindication to bone formation and resorption but, in general, and in its extremes, it makes the repair process different. I think that is clear.

[Slides.]

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I want to harp on this one point, and I am winding down now, believe it or not, that the nature of the host site is critical to the end result. If the host site is programmed to make osteosarcoma, if that is what it is doing, the cells that are recruited locally to replace the bone graft material have already made a decision to make osteosarcoma. No surprise.

If these local cells had been preprogrammed to make fibrous dysplasia, it is very likely that you are going to see the bone graft material, regardless of how good it is, again replaced with fibrous dysplasia. I think we really must keep that in mind as we move ahead in designing our studies.

[Slides.]

In terms of the use of bone graft material and the need for a blood supply, we frequently place bone grafts around implants. The bone graft is not going to obtain its nurturing requirements, its blood vessels and its cells, from either polymethylmethacrylate, plastic or metal.

So if a bone graft, in association with a metallic implant, is to succeed, it must have another route by which it obtains its blood supply and its cells. I think by now that is self-evident.

[Slides.]

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Let me just buzz through some of the other things on my list. Irradiation, we know, influences the characteristics of the local small blood supply, small blood vessels, and, more so, the cells. Surgical technique, as Halstead told us, similarly influences the quality of the tissue and cannot be ignored.

[Slides.]

Other graft factors represent local events. The way we preserve it, the way we size it, shape it, infect it, load it, also have an influence on the events of bone graft incorporation as do the systemic issues of chemotherapy, drugs and, perhaps, even the immunology.

[Slides.]

This is a junction of a bone graft in the host skeleton done in two cases by the same surgeon using the same technique and, in one case, beautiful repair at 12 months and, in the other case, clearly a non-union. These are allogeneic implants, and we very frequently turn to the immune system as the source of reason and rationale explanation for failure. In fact, that may be true.

[Slides.]

Let me end where I started by expressing my opinion that bone grafts and those substitutes we use for bone grafts will undergo a predictable sequence of biologic

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events. It is a cellular circus, if you will, and these cells are modulated by a variety of very, very important factors which emanate, in many cases, from cells other than the osteoblasts and osteoclasts, but the language that they use to speak to each other is mediated by molecules.

[Slides.]

The sequence of activity is influenced by a variety of events at the recipient site and systemically. We know that there are a wide variety of clinical applications that have been associated with successful use of bone graft and bone graft substitutes, and I hope that I have pointed out for you that, in many cases, the reasons for failures are comprehensible, are understandable.

[Slides.]

As we move ahead in our clinical arena, we must not forget that we do have enormous knowledge and potential in understanding these events at a biologic and biomechanical level.

That is where I will leave it for right now.

Thank you.

DR. HANLEY: Thank you.

Speaker No. 2 is Dr. Michael Yaszemski. He will speak to us in tissue engineering of bone and bone products.

Tissue Engineering of Bone and Bone Products

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DR. YASZEMSKI: Good morning. While my slides are being put on, let me say hello and thank you for the invitation to speak.

[Slide.]

My charge and my topic today is tissue engineering of bone and bone products. Now, the panel discussion today is on bone void fillers. Although the use as bone void fillers is one application of tissue engineering of bone and bone products, the entire field encompasses other applications, as well. And we will get into those as we go on.

[Slide.]

I thought I would start by trying a definition of tissue engineering because, as an engineering discipline, it is relatively new. I have been a chemical engineer for 20 years now and, for most of those years, the words "tissue engineering" were not in the engineering lexicon.

It has emerged over the past few years. I think, as a definition, I will offer that tissue engineering is the formation of new tissue by cells when those cells are supported on an appropriate scaffold and supplied with nutrients. That scaffold may be natural scaffold. It may be a polymer. It may be a ceramic.

[Slide.]

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As tissue engineering evolved, as best I can tell, I think that the initial finding that led to this branch of engineering was a demonstration in 1974 that macromolecules could diffuse through porous polymers. Up until that time, it was thought that anything of a macromolecular size, if encased in a polymeric material, would be immobilized and would not move through the material.

With the demonstration that movement was possible through polymeric materials of macromolecules, subsequent work led, then, to work with the interaction of cells and polymers. This culminated in the formation of a new society. The Tissue Engineering Society is new this year and had their inaugural meeting last December.

[Slide.]

There is a research activity in orthopedic surgical applications that includes several things other than bone. There is work going on cartilage and tendon and ligament.

In addition, there are non-orthopedic applications. For example, there is work being done on neo-trachea, neo-liver, neo-pancreas, neo-intestine. For the purposes of today's discussion, we will limit our focus to bone.

[Slide.]

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In general, as Dr. Friedlaender went over, for bone regeneration, several things are necessary: an osteoconductive scaffold that the cells recognize and will attach to; cells, whatever level of differentiation they are when they start toward the process of making bone; and growth factors that are present spatially and temporally in the correct sequence to encourage this bone regeneration to occur.

[Slide.]

For tissue engineering applications, for scaffolds, people have used a variety of materials; synthetic polymers, ceramics and natural polymers have all been used. An example of a natural polymer would be a collagen sponge onto which growth factors or cells are put. Ceramics; two very popular ones are the hydroxyapatite and beta-tricalciumphosphate.

Synthetic polymers are polymers that have, in their structure, something that can cause them to degrade, by and large. Examples are the polyanhydrides, polyesters of various sorts, polyorthoesters, particularly the polyethylhydroxyesters. PGA and polylactic acid--rather polyglycolic acid and their copolymers have received a lot of attention.

[Slide.]

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The basis of the degradation for the scaffold, and I might step back just a second and talk about why the scaffolds have to degrade. As you heard, again in Dr. Friedlaender's talk, this sequence of bone formation progresses through rather predictable stages. Just as you saw in the slide with the methylmethacrylate, where the persistence of the methylmethacrylate will prevent that process from happening, the interaction of the scaffold with the cells and, hence, the new bone, occurs in such a way that it is better if, over time, after the scaffold does its job, it goes away and lets the bone remodel.

The basis for much of the scaffold resorption is hydrolysis of an ester bond, or hydrolysis of an anhydride bond. When the scaffolds are made in the laboratory, they are made such that they are far from equilibrium. Most of the reactions that make polyesters, polyanhydrides, polyphosphazines, like to be monomer, if you will.

They like to be in the small-molecule stage. One has to trick them by a variety of methods such as the exclusion of oxygen, removing the products of polymerization and, in some cases, a water molecule, and keeping them in that stage until they are put back in the body.

Then, once they get into the body and are exposed to water, under a variety of influences such as their

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relative hydrophobicity or hydrophilicity, they will interact with the water and the water will take them back toward equilibrium which is the monomeric state.

[Slide.]

We have talked about scaffolds a little bit. The second component of scaffolds cells and growth factors are the cells. In tissue-engineering strategies to make bone, the cells can be a variety of cells and they can come from a variety of places.

Along the line of differentiation from cells in the marrow up to osteoblasts, these can be harvested. They can be grown on the polymers in the lab and then put back into the host at the time of bone regeneration in the expected site.

On the other hand, the scaffold, itself, can simply be put in and the source of cells can be the body. The strategy in that case is to encourage the cells to migrate from a position in the body to the scaffold and begin to effect their phenotypic function.

[Slide.]

Now we will talk about the third component of scaffold, cells and growth factors, and that is the growth factors. There are a variety of them that are thought to be involved in the bone regeneration process, some more clearly

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elucidated than others. But they have to be delivered somehow to the site.

They can be delivered again in a variety of ways. They can be delivered from the scaffold or from a secondary carrier. I will talk about secondary carriers in a little bit. They have the requirement of being immobilized at the regeneration site.

One can include them in a carrier, deliver it to the regeneration site and then the carrier, perhaps, gets carried away with blood vessels or diffuses away, and the molecule that is needed to direct to formation of bone is not available at the site.

Three that come to mind, I just mentioned. As I said, there are a host of them. But many investigators have done quite a bit of work with transforming growth factor beta, 1 and 2; basic fibroblast growth factor and a variety of bone morphogenic proteins.

[Slide.]

I might also mention, with delivery of the growth factors, some strategies have the growth factors delivered locally; that is, they, perhaps, will put the scaffold and/or the scaffold and cells in a local site and depend upon a local presence of growth factors, either because the site is at the correct stage of normal fracture repair that

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the growth factors would be there or that growth factors that are indigenous to the area of the regenerated site will be depended upon to guide the process.

[Slide.]

I think that the essence of the so-called tissue-engineering strategies are the scaffolds so I would like to spend a little bit of time talking about them. As we discuss devices, tissue-engineering strategies to regenerate bone, be they devices, may include scaffolds alone and depend upon the host to deliver their own cells and deliver their own growth factors or they may deliver cells, growth factors and a scaffold in which instance, the growth factors, perhaps, have come from the host or have been synthesized, or have come from some other host.

The cells may have been previously harvested from the host and expanded in the laboratory which brings up the point for discussion that much of what we are talking about in the bone void filler area is avoiding a secondary surgical site and avoiding a second operation or a second incision.

But, for some of these strategies, to get the cells, one is going to have to harvest them at a separate time from the time of reconstruction in some fashion or other, be it by bone-marrow biopsy or an open procedure, to

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get cells, separate them out and grow them on the scaffolds in the lab.

The scaffolds fall into several categories; polymer foams seem to be the most popular. There is great design flexibility and one can synthesize and design new polymers and then process them into a variety of shapes to serve the functions that are needed.

Porous ceramics; again, the hydroxyapatite and/or tricalcium phosphate. In addition, in some applications, one finds a porous ceramic in combination with a polymer foam such that the polymer foam is then a particulate-reinforced structure usually with the thought that the reinforcing ceramic will provide both some structural strength to the foam and an osteoconductive matrix that the cells will recognize.

Collagen foams have also been used, and there are some studies going on where growth factors are placed directly, for example, in a bovine collagen foam and the delivery of the growth factors, then, is effected by placing the collagen foam in the area of regeneration.

An example would be a posterolateral intertransverse spinous-process fusion with a bovine collagen foam laid across the transverse processes in which the goal is for the two transverse processes to effectively

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fuse together and become one. A growth factor is dripped into the foam with the hopes that that growth factor will then be delivered from the foam.

[Slide.]

When talking about polymer foams, several properties of the foams come to mind and, I think, are relevant to discussion. One is the degradation. Again, we depend upon the foams to degrade so that the bone, hopefully, if and when it forms, can be allowed to remodel along the lines of the stress fields it finds itself in without having the polymer in the way.

The degradation is thought to be mostly, for most of these degradable polymers, via hydrolysis. There is some evidence in the literature that there is enzymatic degradation of some of these polymer foams. There is evidence that proteins attach to them.

Secondly, porosity and interconnectivity are two features of the foams that are often under investigation. They are sort of two edges of a sword, if you will. The foams need to be porous so that there are spaces inside them for cells to attach and for blood vessels to grow in and supply the cells with nutrients.

However, every increase in porosity is traded off by a decrease in strength. For bone void filler

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applications of these polymer foams, cells and growth factors, when the patient needs to get on with their rehabilitation, it is desirous that the construct have a certain strength and that we can get on with the rehab of the patient.

That strength initially has to be supplied entirely by the device. As bone and vessels grow in and the device degrades, the more porous the device is initially, in general, the less its strength is initially and, perhaps, the nadir of strength during degradation and bone ingrowth might be less than is necessary for the mechanical function of the part.

Cell attachment. Osteoblasts are anchorage-dependent cells. They must attach to the polymer foam to express their differentiated function. And, to a variety of the polymer foams that have been used, osteoblasts seem to attach well.

Strategies are available with polymer foams to enhance that. Some of the strategies, for example, include chemical derivation of the polymer foams. It is possible, and it has been done, to covalently bind peptide sequences that are cell-attachment recognition sequences to polymer foams and have them present on the surface in an effort to enhance the attachment of osteoblasts to them.

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[Slide.]

I think I would like--since this is the form for devices and testing and evaluation, I wanted to touch briefly on testing of tissue-engineering constructs, devices, if you will. I will separate them into in vitro and in vivo.

For most of these constructs, they involve the synthesis of a novel polymer. Like any new material, it needs to be characterized. So much of the in vitro analysis deals with methods of synthesis and characterization. Alternate routes of synthesis that may or may not use different solvents, different catalysts, are explored because, in general, the solvents and catalysts, if used, have to be removed prior to thinking about using these in vivo.

We need to characterize them to find out exactly what is in them chemically after we make them and before we think about using them in vivo.

Mechanical testing, since we are trying to replace the mechanical function of a skeletal part, is an integral part of the in vitro analysis of scaffolds. The mechanical testing can be done in several different ways. On a more basic scale, the polymer, itself, can be tested. Polymers in, perhaps, filament form can be tested via dynamic

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mechanical analysis for their tensile properties irrespective of the properties of the structure into which they are made when they are processed.

However, those structures are then tested and the polymeric structures can be defined by such things as their compressive strength, their bending strength, their compressive and flexural modulus.

Also, they are typically, or frequently, I should say, placed in simulated in vivo environments and allowed to degrade and then degradation profiles are obtained to assess that, in the absence of ingrowth and vessels and cells, what is the strength history of these as they are exposed to hydrolysis.

Other in vitro studies that occur with most of these novel polymers are studies of cell attachment, cell proliferation, cell migration on the polymer either in a monolayer or in a three-dimensional sense, an expression of a phenotype.

In the case of the osteoblasts that we are working with, I am not sure that, and perhaps someone who is expert could come up and tell me if there is a certainty about it, but my understanding is it is very difficult to be certain that a cell is, in fact, an osteoblast. And we check whether it is an osteoblast by checking whether it does what

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we expect an osteoblast to do.

Things we can check are whether these cells in vitro make type 1 collagen, whether they make osteocalcin, whether they synthesize cyclic ANP in response to parathyroid hormone stimulus.

[Slide.]

In vivo, we want to see if it works. Dr. Friedlaender, again, mentioned the critical size defect. I will just say, again, that is a skeletal defect that will not heal in the lifetime of the animal without something happening to it.

Examples of that are in the literature are calvarial defects. These have been well described in a variety of species. For orthopedic applications, however, I think I will step up and say that it is probably more common to assess a long-bone segmental defect. There are a variety of critical-sized long-bone segmental-defect models for use.

As I mentioned before, the differentiation between tissue-engineering strategies being bone void fillers and being used for other reasons; I think the long-bone segmental defect spans both of these very nicely in that it is a bone void. It includes both trabecular and cortical bone, but it is just a touch away from replacing a part of the skeletal with a construct, a device, that is

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essentially, if you will, a bone made to order; that is, if we can duplicate the geometry and the size of a missing piece of bone and see if we can encourage that to happen.

I put prevascularization analysis down to emphasize that sometimes the cells aren't all put in in the lab. We have found, for instance, in our own work, in the migration of osteoblasts on three-dimensional scaffolds, there is a distance in from the surface past which we have very much difficulty getting them to grow.

It is on the order of 170 to 200 microns. We find on analysis, then, that the interior of these devices is well vascularized and filled with typical granulation tissue. Whether the timing is wrong and the osteoblasts in the center die before the vascular supply gets in or whether the vascular supply and subsequent granulation tissue is too abundant and fills up the available pore spaces, I don't think I can say right now.

But some efforts are aimed at a prevascularizing scaffoldable and having them be formed in such a way that they then can demonstrate or possess a porosity after the vascular supply is in and before they are seeded with cells. Several strategies are in effect to have scaffolds prevascularized and then subsequently seeded with cells different from the in vitro pre-implant cell seeding.

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[Slide.]

The three-dimensional matrix is what I just discussed. I mention the rib-bed model to emphasize again that sometimes the scaffolds use host cells and host growth factors. One of the tests we have done was to put a scaffold on the periosteum of an excised rib bed in a sheep model and come back a little bit later.

We have found, in this particular study, that the scaffold, presumably supplied with growth factors and cells by the periosteum against which we put it, was well filled with bone and that it had revascularized, in this case, since it was a rib bed, from the intercostal artery and vein.

That artery and vein were then available to harvest with the new piece of bone and transplant to a different site. So, again, there are a variety of combinations of tissue-engineering strategies that range from supplying growth factors, cells and scaffolds all with the device to simply supplying the scaffold in a place and in a temporal fashion where the host can supply the cells and growth factors.

[Slide.]

Lastly, I want to comment a little on scaffold and growth factor interactions, for those cases where we might

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decide to supply the growth factor with the scaffold. I mentioned that BNP, for example, has been dripped into collagen sponges and then, subsequently, delivered from them.

Problems with growth factors in the tissue-engineering constructs are that one needs to keep the growth factor near the construct. Growth factors have been successfully put into microspheres and the controlled release kinetics worked out; that is, the polymer microsphere, if it can be encouraged to degrade from the surface, will slowly recede and the growth factor that is encapsulated within it can be delivered both by diffusion of that growth factor through the polymer and combined with the recession of the polymer by its surface degradation.

The polymer microspheres, however, need to stay where you put them. If you simply, for instance, sprinkle them at the site where you want them to be, they are going to diffuse away. They are going to be carried away with blood and, then, your intended delivery of the growth factors is probably going to be less than ideal.

Strategies include making a three-dimensional porous polymer matrix into which the polymer microsphere can be trapped and/or attached via either electrostatic or covalent means.

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So, once again, as we discuss the loading of growth factors, we need to be cognizant of the fact that we can put them in something and deliver them but we have to also try to keep them at the site we want them to be at.

[Slide.]

In summary, let me say that tissue-engineering devices for bone regeneration will likely contain some combination of a polymer or a ceramic scaffold, autologous cells or growth factors. One of the questions that I have heard come up again and again as I was preparing for this is do we call it a device or a biologic.

In certain instances, cells are harvested, cultured outside the body, expanded in numbers, attached to scaffolds outside the body and then put back in. In some instances, the growth factors are synthetically made and then put back in.

In some instances, the cells and growth factors are purely autologous and the only implant is the scaffold. I will leave that up to you experts to decide what the answer is. If I could offer my own thoughts; my thoughts are that it more closely resembles a device than a biologic.

Thank you for your time and for the opportunity to speak to you.

DR. HANLEY: Thank you.

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Our next speaker is Dr. Joseph Lane. He is going to speak on ideal study design for experimental trials utilizing bone void fillers.

Ideal Study Design for Experimental Trials

Utilizing Bone Void Fillers

DR. LANE: Good morning. I want to thank Ed for allowing me to come here. This is my first time at this kind of meeting and I am going to be a little more casual because I would like to engender a little discussion here.

[Slide.]

I was charged with the title, Ideal Study Design for Experiment Trials using Bone Void Filler. I would like to ask the panel to eliminate that term, bone void filler, because as we will go through the process, I can certainly fill this with methylmethacrylate and get rid of the void. But, as we have seen by Gary Friedlaender, this is a totally unacceptable methodology because unless it is osteointegrated with the bone, ultimately, if the patient lives more than a few months, it will ultimately fail.

So, therefore, I think that if you are going to get material, it really has to have a different goal. Its goal, really, has to be osteointegration and play a functional role with that bone.

It has to do it, in fact, better than doing

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nothing and, at least hopefully, be as good as autogenous graft.

[Slide.]

I keep using this word "filler," but it makes me extremely uncomfortable throughout this discussion. But, basically, what we are looking for in any kind of material that we place in are clearly osteoconduction, induction, progenitor cells and structure.

Since this is a device panel, it has traditionally been looking at that latter term, "structure." I think we have to take a look at the role of this conduction and induction in cells because they will play a very critical role and we must have a user-friendly material which allows this processes to take place.

Either it is going to have to provide it, itself, or work in partnership with the local environment to achieve that particular goal.

[Slide.]

Let's go over this osteoconduction business a little bit. The first thing that you have to recognize is that bone, unless you are looking at cortical bone, is only 22 percent of the volume, and the marrow cavity is filled with bone. Almost 80 percent of it is filled by marrow in other areas.

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So even if it were never removed and took up 20 percent, it would be of little consequence to the bone because the bone would bypass it. There is still plenty of volume but if you put a material in there which takes up 60, 70 percent of the space and is not remodeled, this will have mechanical problems.

But we are talking, now, about trabecular bone. We are not talking about cortical bone. Cortical bone, on the other hand, takes up all the space. If you put in an application where it is going to take and participate in a cortical area, then that must be integrated and must be removed or not compromise a mechanical area.

So anatomical location is absolutely critical; is this a metaphyseal application, is this a cortical application, and, also, where is it in the particular bone. We will get into things like tension, torque, et cetera, which plays a very critical role.

It is on the surface in which osteoblasts--now, these can be mesenchymal stem cells which ultimately form osteoblasts, or it can be osteoblasts, but, if you don't remove it, you are going to have to form a bony, interdigitation with this material that is in a friendly, useful way and go throughout all surfaces.

Now, if there are potential surfaces deep within

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this material but they are not connected to the outer surface, that means the body is going to have to bore holes into that particular area. That takes a long process. I will tell you that if it has to go more than a couple of millimeters, it won't get in there. It will never penetrate into that kind of distance as far as you can handle it.

So, basically, you are going to be left with a material having to provide not only compressor strength but tensile strength if you do not replace it and you cannot penetrate far into it.

So I think a very critical element that you have to worry about is do you have connectivity and how hard is it for the bone, in its remodeling phase, to get into the particular device that you are using.

Now, resorption and remodeling; well, first of all, I am not even sure these are "resorbed." They are attacked by foreign-body giant cells. These are different cells than osteoclasts. Osteoclasts identify inhibins, integrins, on the surface where they then bind to.

Now, certainly, we just heard our prior speaker say he can fool them by sticking these integrins on the edge and maybe the body will think it is a surface. But most of this is carried out by foreign-body giant cells.

So the process of removal is a very complex one

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and will be dependent on the matrix you use and the process by which it goes. I can tell you from my own personal experience, if you make a very toxic local environment, you will inhibit the growth factors. We have seen this in many of our experiments.

So we are talking about anatomy, the surface, does it have connection, are the pores available to the cells and is this really, truly, osteoclastic resorption or is the foreign-body giant-cell manipulation.

[Slide.]

The next one, in terms of osteoinduction--there is going to be a process that is going to have to drive this whole integration in. Now, certainly, it is almost impossible unless you have a transgenic animal, to get rid of TGF beta. It is always ubiquitous in the body. But, on the other hand, there are other growth factors that play a very critical role.

And, is this a user-friendly material, meaning will it adsorb local growth factors from the environment or will it, in fact, play no particular role. And will it hold growth factors if you add it. We are in an evolving world now where people are adding growth factors to the area.

What are the releasing properties of those growth factors either locally gathered up or provided, and, also,

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how hard is it to get a vascular invasion. Vascular invasion is very critical because the lamellar bone which is deposited usually comes from the pericytes that are coming with the invading vessels.

The stem cells may produce the first woven bone. Lamella, in remodeling, is very closely related to the vessels. If the vessels cannot penetrate into this material, you will not remodel along lines of stress and, ultimately, this material will fail. So it has to be vessel-friendly.

[Slide.]

Now we get back to those osteoprogenitor cells. For instance, can you be a repository of osteoprogenitor cells? Is this user-friendly? Can you load this material up with progenitor cells? If you do not have a ceramic or a material or a polymer or whatever that has interdigitated connectivity, you just put the cells on the surface. They are not in the body of that material.

[Slide.]

If you get it in, will those cells survive while they are waiting for the blood vessel to come in. So how thick are those cells? How close to the surface? What is the shape of this particular material and is it user-friendly, and how well are they invaded.

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I would charge the panel to look at the dynamics of cellular invasion. You can't do it in humans, necessarily, but you certainly would like to have preclinical trials with animals that demonstrate the vascular invasion into this particular process, in the cell penetration.

[Slide.]

This is a device panel so you guys are very comfortable in dealing with structure. But, you know, there are different kinds of materials that we are talking about. We have two of the speakers today. Bone is a wonderful material. I can tolerate compression, tension, torque, and it has the ability to repair itself very rapidly when you change the mechanical environment which is being faced.

As Gary Friedlaender showed, you will then remodel or model this graft or the fracture healing to accommodate the varying changes in the mechanical environment.

Now, ceramics, unless there is something out there that I don't know about, I just think it basically, it largely has mechanical properties in terms of compression. So if you place it in an environment that sees torque or tension, it is not going to function, guys. Therefore, you are going to have to coinsert it with some other device which is going to protect it while this process basically

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goes on.

Obviously, most of the biodegradable materials, whether they are natural or synthetic, it is very hard for them to provide enough mechanical compressor strength. They are far less than trabecular bone, let alone cortical bone. So if you think that they are going to provide mechanical strength, they aren't. They can't unless you profoundly alter their properties.

It is not that they can't be made, but the ones that are currently made do not have those particular properties.

If we take a look back at some of the material that Gary talked about, and this is very important for us to remember in terms of this material--Gary showed in Burkhordt's work, that, in dogs, you lose about one-third of the strength of a cortical strut and it takes up to 18 months to return to normal.

That is a dog. That is not a 68-year-old elderly--that is not elderly--a 75-year-old elderly individual--68 gets younger every day. 68 is a teenager in my practice. But, basically, the question is how long does it take for this to regain its particular strength.

I have recalculated Bill Ennican's data on his non-vascularized material, and if you have a

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non-vascularized strut that is over 12 centimeters, he has a 58 percent fracture rate. He has a fatigue fracture rate. If you do the same process for vascularized struts, it is 22 percent, at that particular distance.

So, no matter what you are putting in, it does get weaker. The way that these things resolve is that the body will attack it, heal it and then will remodel it. That is with autogenous bone. That is a target, how good are the ceramics or these other materials. I dare say they are going to be much weaker and it is going to take a long time for them to regain these particular strengths.

Therefore, I think that as you develop your models, if you have discontinuity, you are going to have to provide fixation at the same time you use your--because you are asking these devices to do something that they cannot possibly provide. They cannot possibly provide this.

[Slide.]

Now, if we take a look at some of these things, for instance like the allograft ring which is used routinely in spinal interbody fusion, this functions, basically under compression but most of us will add autogenous graft inside the ring waiting for the face.

And we have learned we do not use those rings without fixation because they will be displaced or placed

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into a new position. I can tell you that all these new rings that are being made with the ceramic that you fill with bone graft and put into the body, I think you better look at the histology of those things very carefully.

My view is that a big chunk of those never really get osteosynthesized. There is a little non-union rate. We have actually looked at long-term compression, and you get subsidence of the vertebral body meaning it is moving event that may never really have been integrated as well. Particularly if the holes are very tiny, you are asking very high charges of those particular rings.

I love those rings, but I am just saying you better put a fixation at the same time.

In terms of ceramics, they, again, will be under compression. And they will have to hv protection for torque and bending until the body comes in. So, again, if you apply these, you are going to have to put them in a user-friendly environment which allows osteointegration to protect these particular devices. They are only there for a time.

[Slide.]

Now, I would like to make a comment about bone and failure. I hate to do this in front of Seth because he is such a star in this stuff, but, basically, lamellar bone

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will not tolerate anything over a 3 percent strain. If you do over that, the bone will fatigue.

So, therefore, if you put a device in and more than 3 percent strain takes place with that device, the bone will fail first before the device is seen. So, when you put a ceramic in, unless you are absolutely guaranteed in your mind that you have wedged it in such a way that will not permit 3 percent strain, you will have failure of the adjacent bone such as around a void before you come in contact with the ceramic.

Since ceramics, again, have to heal by metaplastic bone formation, they must be so protected that they will not tolerate more than a 3 percent strain. Otherwise, they will go on to non-union. So, most utilizations of ceramics, if you have motion, you have got to provide absolute fixation. Otherwise, these ceramics will not be integrated within that particular environment.

[Slide.]

This brings up some of the questions that perplex me; for instance, the hole in bone, and question of voids. Do we need a void filler? Well, we make voids all the time when we take out screws and we have learned we don't have to fill them with bone graft.

The body will bypass that hole within six to eight

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weeks. For instance, we can have terrible tibial fracture healing, but it was amazing how we will get around major defects by sort of developing a mechanical force through remodeling.

So, basically, if you use a filler for a hole in bone and it takes more than eight weeks to get integrated within that hole, the body would have solved the whole problem by itself not even using the device. So this raises the issue when you look at your models, whether in animals or in humans, do you have a control of nothing and do you have a control of autogenous graft.

Obviously, these are the kinds of studies that you are going to do, preclinical trials, because you are not going to do this in humans. We have learned the lesson that what we thought is important may not be. The Japanese looked at the study using steroids in holes, injecting steroids. And they said--Scialiatti said, "It is a very wonderful way to take care of these unicameral cysts."

They took a group of patients and just made holes and found there was no difference whether or not they got the steroids

So, basically, I think that the panel is charged by very carefully looking at what the controls are because it may, in fact, be of little benefit to use these

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materials. I would say if you are just going to use ceramics to fill a couple of holes in bone, it may not be very important. The body may not need it because they will just go past and bypass the area.

[Slide.]

This really brings up the superb study done by Ed Chou and Frank Frassica. What they did is they took a defect in the condyles of dogs and they drilled a hole, carved it out, and packed it to the greatest strength that they could with methylmethacrylate.

Here is superpressure. Then they went ahead and tested it mechanically and found that, whether or not they added the methylmethacrylate, it didn't make any difference on the fracture of the condyle because the bone went through more than 3 percent strain before it came in contact with that methylmethacrylate.

Methylmethacrylate is our toughest material. And this was acutely. So the question is what are these things really basically accomplishing. What it did show is that it didn't collapse all the way down because you bumped into the methylmethacrylate.

Dr. Friedlaender and I have seen this with giant-cell tumors. It prevents collapse, but you can't prevent the fracture. It is almost impossible. I don't

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know how to do it to avoid that.

[Slide.]

Now, let's look at the anatomical locations. What I would dare say for the panel, one of the questions that came up, was is one thing good for everything. I would say no. I think that there are different mechanical loads. If we look at the kinds of areas where you use bone grafts, such as the intervertebral disc, anterior, this is largely under compression.

You may be able to use a device which is largely in compression which allows some digitation. Diaphysis sees torque, bending, tension and compression. I dare say that many of the ceramics we have will not meet the goal there unless it is protected--it is not that you can't use it, but you are going to have to, then, do it in the setting of the device and something that will lead you, ultimately, to a resorption or remodeling along these lines.

Metaphysis is largely in compression. That has had the best success for many of these ceramics today; the tibial plateau, the distal radius--superb applications of these ceramics.

In terms of where most bone graft is today is in spine fusion, to be very truthful. That is a different situation. There it is under bending and tension. Ceramics

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don't function well in that area unless they are part of a large pattern which includes the rapid production of bone at that particular time.

[Slide.]

So, what would I look at in a filler? I would say there has to be incorporation and integration. It has to permit modeling to meet the loads. Clearly, if anything which just sits there as a stick in the log and which is not doing it--it has to have the ability to not compromise remodeling by filling the defect, like being stuck on the cortex and just not being able to be able to move.

I think that we have to recognize that in most applications--most applications--there is going to have to be the coinserction or fixation. This is going to be a challenge because the fixation may blind you to the ability of efficacy. That makes it very hard for the judger to determine if this is really working.

You can do it in an animal because you can always mechanically test it. But when you look in the human, it is going to be extremely difficult because the fixation has to be part of the process. But, because it is there, you are not going to see motion. This is going to make it very difficult for you guys to judge this.

[Slide.]

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Then, the question is, should it be a block or is it granular. There are settings where blocks are important such as the vertebral body. But in areas where you want an encouragement of bone to occur as soon as possible, it may do better in a granular form or some other kind of a matrix, a loose weave or whatever they call it, a foam or these other kinds of processes.

[Slide.]

The other thing is we have to be--it is obvious that today the big surge is in stem cells, ex vivo expansion of stem cells, and also the use of growth factors. So it has to be user-friendly for both those components because we are going to be either using our body or we are going to be providing it. We have to develop a system that is out there and a good receiver of that area.

[Slide.]

So what I think is an ideal thing? I think it has to be porous and connected. I think these pores cannot be isolated pores, but they clearly have to be connected pores so they can get the body through it.

It has to allow bone interdigitation, integration, et cetera. If it is going to be compressive, it should share the compressive load but you are asking too much to say it should take all the compressive load. If it doesn't

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do much of the compression, I am not worried because I don't think very much of that mechanical thing anyhow because I think that it really fails so dismally in terms of tension and torque that, as an orthopedist, I would put a fixation device in there. I would not depend on that particular area.

So I wouldn't push too much on it and it clearly has no role in tension and torque. The sites, therefore, that I would test as a unit, and I think that you should require, would be the metaphysis. This is a metaphysis without continuity or with continuity.

If you have got it with continuity, the applications may be arthroplasty or something like that. But basically discontinuity would be fractures. Therefore, that should be one area you are testing.

The same with the diaphysis. Is this a diaphyseal hole with continuity or without continuity. Again, fractures, obviously, are discontinuity.

Arthrodesis. I think here, you have got two kinds of arthrodesis. I think if they are going to claim for the spine, it should be the interbody anterior which is largely under compression and may be user-friendly in these little chambers that are now being established. And does that ultimately get remodeled and really go to osteosynthesis and

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the posterior spine fusion which may be a very different kind of three-dimensional array which has to be set up.

Clearly the arthroplasty, filling holes around joint replacement areas. When you have revision joints, is this a user-friendly material and how do you integrate the prosthesis into this particular area? This is a very challenging area.

[Slide.]

What kind of animals? I will make some comments about animals. Obviously, rodents are "el cheapo" and easy to do. But, you know, a femur of a rodent is only 3 millimeters in diameter. You take a granule which is 4. It is bigger than the femur. It has a very different pathway than in a human where 3 millimeters doesn't seem to be very much.

And, of course, with a rodent, as long as the bones are the same room or building, they will heal. So you have to recognize that it has to go to a different kind of an animal.

The sheep and the dog are--now, I know that Doug Jackson is a big goat person. But, basically, the most experience has been done on sheep and dogs. They have advantages and disadvantages. I would clearly never do a dose-response curve on a dog. We would never get through

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our animals.

So I think you have got to look at the ethics of some of those testings, et cetera. Again, the monkey is exquisitely expensive. You are never going to get statistical numbers in a monkey because you can't do 50 monkeys. You are asking costs that are out of sight.

But I think you can check toxicology and get a feeling that it is going along as anticipated within the monkey. I think there are always going to be two or three monkeys per whatever you are testing. But you can't do 50. It is difficult.

Finally, there is the human experiment. Again, the human experiment, I would dare say no graft, autograft and then whatever you are doing. I think you have to be very careful in that particular area.

[Slide.]

Now, the critical defects. We have heard about the skull and the long bones. They are areas. But I am not so interested in defects that do not have discontinuity. There are so few tumors out there. You can make a product for a tumor, I guess, but we are talking big business. Big business is fractures, arthroplasty, and spine fusion.

So I think the model should be directed at those particular areas. Therefore, I have liked the long bones as

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my particular models, the radius, the ulna. You can use instrumentation or not. The tibia, the femur and the mandible have been used because they are different kinds of applications.

In terms of the spine, you can usually use the rodent, with a rabbit spine, the bone model or the Sandu model, which is the dog model. I think you can use those particular areas.

[Slide.]

In terms of the outcome, we are going to hear about radiographic outcome. But I think there are different kinds of things and I would encourage at least preclinical information about the three things; do you fill the defect, is there union, and is there remodeling.

I think you should know about it. I am not saying that you have to remodel the material away because, if it is in the middle of the metaphysis and it never remodels, I am not sure it makes much difference. It makes a big difference, though, in the diaphysis. You want to know your union rate.

In a mechanical, you really have got to look at something that includes torque or bending because these devices fail in tension and, therefore, if you only test in the compression, you may be fooled. I think you have got to

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include something that has a tensile component in the testing device.

Then, in the histology, I am really interested in the amount, the quality, turnover parameters, and is this a foreign-body giant-cell reaction or is this an osteoclast resorption. I am not saying that you can't have a foreign body, but if you produce factors which inhibit growth factors--you produce a low pH and it is going to inhibit the growth factors, we have to know about it because it is going to help the people coming along with their growth-factor mix.

That is one of the big programs with the biodegradables is that they get a very low pH at a certain time--not all of them, but some of them. You want to know when they are going to degrade and how they are going to degrade and what is going on in that particular area.

[Slide.]

Lastly, is the follow up. There are two ways you can test this. You can say, do I end up as good as autogenous graft or can I do it faster. What is my success rate of union, or whatever, if that is your goal. And the other question is is it faster. If it is faster, if they are going to claim it is faster, if it is two days faster, that may be statistical important but it is clinically

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irrelevant.

So you have got to get some kind of testing by these people who are going to use it. If they are going to give that statement, you have got to have a meaningful statement. Therefore, when you do your power, it should be a clinically relevant power, not a--if you take 10,000 patients to show that laminar-flow room makes a difference--I want to know is it 100 patients and can you see a difference.

If it doesn't show in a 100 patients, as a clinician--I think it may be very interesting biologically but probably not too relevant, particularly to my HMO. It will not be interesting to them.

[Slide.]

I think that the other problem that is a real challenge to the panel is since most of these will not have adequate mechanical properties, what is going to happen is they are going to put fixation in. This is a profoundly major challenge to the panel, particular spine fusion.

Is it union or not? It is hard enough when you are there at the operative scene to ask the radiologist to make this determination when the fixation is--you have to wear sun glasses because there is so much metal in there--it is extremely difficult to make these determinations.

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Conversely, to ask a spine surgeon not to use instrumentation is not ethical today. So it is a very difficult problem for the panel, very difficult.

[Slide.]

My closing comments. I don't like historical controls. It is very nice to get you thinking but I think you have got to include a common group at the same time, a control population. Your methods change. If you try to look at the orthopedic literature, it is grim, sometimes, in terms of looking the way it does. We don't have the materials. I think prospectively is the way to do it.

I think there is going to have to be autogenous controls because that is what you are comparing against, autogenous bone graft. In certain applications, I think one of the controls is going to be no graft--no graft--because that may be an indication, particularly with the wonderful instrumentation of the traumatologists today.

They think they can get enough material just reaming and putting a nail in. Therefore, it may heal just without doing anything. They are really getting very good.

Then, of course, there are the type 1 and type 2 errors. What I am concerned about is showing equality to autogenous bone graft. It is like the old concept, you guys know if you do three patients, use treatment A on three

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patients and treatment B--and if you kill everybody in B and don't do them in A, they are equivalent because there is no statistical difference.

I think that you are going to have to be very tough, thinking in your mind what your control numbers are because if you are going to look for equality, you have got to look for it. But I think there are other points besides healing; time to union, pain, function.

I would build into your panels function because one of my biggest problems with autogenous graft, 8 percent of these people are just so mad at me for taking the bone graft--their hip hurts, their something hurts. Yes, it has healed. I got a great union, but they are miserable because of where I have taken my graft site.

So it may use other parameters for efficacy; speed, time, hospitalization. Did they spend an extra day in the hospital? Those are the kinds of parameters you may not make as your primary outcome, but it may be a secondary outcome. I think you have got to start putting those components into the vehicle.

With Swionkowsky's new outcome program and some of these other things that are out there, I think you can begin to start moving toward using those methods.

So my final questions are, if you are going to use

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the material--old versus young. Young kids will heal if they are in the same room. Old people have lots of problems. Gary identified a whole bunch of them.

Are you looking at how fast it heals or does it heal? You have got problems if you use spine. Is it bilateral or is it unilateral? If you put it on one side and you put the test on the other, do they talk to each other? It is very hard.

If you think this is builder-up of autogenous graft, maybe you have given so much graft that it wasn't even necessary and half graft is just as good a full graft. So you have got to be careful in your controls, what do you mean by expanding bone graft.

Is there resorption, is there integration, is it site specific or general? I think that it is a challenge to the panel, but I think there are differences between the metaphysis, diaphysis, anterior spine, posterior spine and arthroplasty. I think they would have to show you why it is generalizable, but they really should be able to show that what they are saying in one is available for another.

Thanks a lot.

DR. HANLEY: Thank you Dr. Lane.

It is 11 o'clock. I think we will take a five to ten-minute break here, then reassemble and finish up the

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rest of the morning. Thank you.

[Break.]

DR. HANLEY: Welcome to the resumption of our presentations. Our next speaker is Dr. Daniel Rosenthal who will speak to us about radiological endpoints for clinical trials utilizing autograft or allograft bone and synthetic bone void fillers.

**Radiological Endpoints for Clinical Trials Utilizing
Auto or Allograft Bone versus Synthetic Bone Void Fillers**

DR. ROSENTHAL: I don't know if I am feeling feisty today or what the problem is, but I am going to start off by disagreeing with Dr. Lane which I know is not a good idea. But I would ask that the FDA not remove the words "bone void fillers" because that would leave a hole in that slide and I have to fill it with something.

The other thing is that I noticed that the morning got off to a quick start and so we are actually ahead of our schedule. That leads me with about double the time I was scheduled for and now that is a void that I am going to try not to fill because we are going to have lunch, and that is a more desirable form of void filling, anyway.

[Slides.]

We could say that there are five primary reasons why one would choose to use imaging studies for following up

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these types of questions. They are listed there on the right side of the screen. It is my prejudice that the need for evaluating such things as healing, incorporation and vascularization, as we will come to in a minute, really grows out of the fact that we do not have perfect faith in the mechanical function of the combination of the bone void filler and whatever hardware fixation is used in conjunction with it.

If we did, if we were confident that the mechanical function was perfect, then it would probably not be necessary to evaluate these other things.

That may not be the opinion of many of the academics who would like to see restoration of normal anatomy. But, for the most part, the function of these things is mechanical and if the mechanical function is perfect, the other things really become secondary. But since they are not, and since they are unlikely to be for the foreseeable future, we do have to look at the other aspects of incorporation.

Radiography, conventional radiography, is the least expensive of all of the imaging modalities that are available to us. It is the oldest, the most widespread, the most widely available and it is a routine part of the patient care for most of these patients and, therefore, will

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probably be used most often for evaluating these types of implants.

[Slides.]

I would caution, though, that routine radiography is not a simple tool. The interpretation of the radiographs is subject to quite a few artifacts of the way the examination is created. I will list a few of them here. There are projection effects of angulation. For example, depending on the rotation of the femur, the femoral neck-shaft angle, will appear different as you see in these different images here.

There are overlap effects that make it very difficult to evaluate certain anatomic sites, particularly the spine and the pelvis. And there are magnification effects which are very pervasive and can vary from one examination to another and can also be quite relevant to assessing the cortical thickness and the size of implanted bone.

There are also, in some cases surprising, effects of positioning. For example, in some anatomic sites, it has been shown that subtle differences in positioning, how the radiograph is initially produced, can even result in variations in the apparent relative length of bones such as, for example, the radius and ulna in evaluating fractures of

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the radius, that relative radioulnar length is an artifact, to some degree, of the position of the film. And the variation can be up to three or four millimeters, depending on how the film is taken.

That may be a surprising thing to a person who does not deal with this daily. Another surprising fact, perhaps, is there is a widespread belief that orthogonal plane films, which is to say two films taken at 90-degree angles to each other, are sufficient to evaluate whether a structure is within bone or not within bone. This is untrue.

Here is a perfect example of it. Here is a screw which was placed through the neck of the femur, for the trochanter and the head but outside the neck of the femur, and, on two orthogonal radiographs, appears to be within the femur.

In fact, it can be shown that there is a mathematical relationship between the number of views, the location of the apparent pin and the probably that it is actually within bone. So this observation is highly relevant to follow-up examinations which attempt to assess the position of anything that is placed within a bone.

[Slides.]

Now, radiography, though, can reveal the internal

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structure of any of the bone void fillers that is placed. Over time, there is a tendency for graft architecture to be changed due to the complex biological mechanisms that have already been described. There are progressive mechanical forces that can lead to compression.

There is progressive ingrowth of vascularization and also new bone formation that can lead to apposition. In fact, there is a tendency toward resorption of the foreign material.

So, in one study, for example, it is shown that heterograft, placed in the bone, gradually condenses and gets to look more and more like allograft, apparently indicating incorporation. This density increase is apparently subject to mechanical forces. For example, in the mandible where a lot of these implants are used, it can be shown that the loss of the implant over time is inversely related to the mechanical stresses to which the implant, itself, is subject.

However, implant resorption may also be a beneficial effect that can be visible over time. For example, in this instance here. This is an acute radiograph taken after this filler was implanted here. The radiograph on the right shows the same wrist three years later.

What we can see in the time interval is that there

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has been almost perfect remodeling of the fracture defect and, one would guess, perhaps a very slight, not completely persuasive, but very slight tendency towards resorption of the implant.

One can see that much more strikingly in other examples as I will show you in this next case here.

This is an acute film, another fracture patient. I show it because I want you to observe the soft tissues in front of and behind the bone as well as the fracture, itself.

[Slides.]

This is the same patient after reduction of the fracture and implant with this material. One can see that some of the material has extruded onto the volar surface of the wrist here in this three-month film. Three years later, one can see that it is gone so that the body, in this case, has had the ability to resorb the material that was extruded out of the bone into the soft tissues in an area where, at least in this patient, it did no harm.

[Slides.]

One can also observe, in this same patient, progressive resorption of the implanted material, itself, over time. One can see here quite a large amount of this material here. It is a hydroxyapatite material. And then

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one can see, three years later, that there is much, much less.

This is a qualitative judgment but I think that it is persuasive enough on the radiograph so that everyone would agree. But an attempt to quantify it, to tell you exactly how much is resorbed, would be extremely difficult from these radiographs. I would just point that out.

[Slides.]

It doesn't always work this well. We have seen a number of instances in which the implanted material was resorbed, to be sure, as, for example, in this case. You can see a film here. I do not have the acute films. This patient was already quite a ways out from the initial repair.

But we see the implanted material here. And then, three years later, we see that a large portion of the implant has been resorbed. But we also see that some of the implant has been extruded. So, for example, one sees above the base of the navicula, a small amount of this material which was not present on the film done years earlier.

So what we have here is a combination of resorption and some degree of fragmentation extrusion of the material into the soft tissue. So this is just the reverse pattern that we saw in the first instance.

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So these are the plane film findings.

[Slides.]

We also see this, despite the fact that the reports have been highly favorable for the trials of these patients. We have seen a number of examples in which the implants have not led to a good outcome. This is one of them. A certain amount of radiopacity is visible in the central part of bone here. You can see it, barely visible, hidden by all of this callous.

This is an obvious nonunion of a fracture of the femur which, at the time it was taken down, replaced, there was a large amount of material that was described as looking like toothpaste in the fracture void which had failed to heal over several years.

So this is radiography is good for. You see the internal architecture of the material. You can see the alignment, if you do it carefully. And you can see evidence of union, to some degree.

However, radiographs have been used to evaluate fracture healing, now, for 100 years. The X-ray was discovered in 1986 and one of the first things that it was applied to was fracture healing. The sequence and the approximately timing of the healing events, as they are visible on the X-ray, is very well known.

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However, individual variation from patient to patient is extremely large and, further, the nature of the phenomena that are observed on radiographs vary from individual to individual depending on the site, the age of the patient, the fixation and so on.

So, for example, the visibility of a callous may be a good sign or it may not be a good sign. Here is an obvious example of a patient with an enormous amount of hyperplastic callous which has failed to unite. So what I am leading up to is that there is not standard satisfactory objective method to quantify the extent of healing from radiography.

That, unfortunately, is the case. One can get a general sense. But to determine whether a fracture is, at any given time, further along towards healing is extremely difficult. Because of this, a great variety of different techniques have been invented to attempt to look at it, and they include some non-imaging techniques as well as some imaging techniques.

For example, resonance frequency methods, impedance methods, have been used to look at propagation of a shock wave through a bone, basically. This method has some promising data but it has not been generally accepted as a tool partly because there are individual variations due

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to soft tissues and because it is not suitable for all sites. It is only suitable for a site to which you can apply such a force.

The speed of ultrasound transmission through a bone has also been used as a method of assessing healing in a quantitative sense. Unfortunately, again, the variability of ultrasound transmission speed from individual to individual is considerable. Although you can show that the speed of ultrasound transmission will drop after fracture and then increase to approximately 95 percent of so of its normal size within a year, there is considerable variation and I think that this technique still is not ready for general clinical application.

People have used a technique called X-ray photodensitometry in which, basically, a radiograph is exposed and the blackness of the radiograph is compared to the blackness of a step wedge or other type of standard that is included in the film. This is a very old technique. It has been largely discarded by the world of osteoporosis studies from which many of these techniques are derived because it is subject to the spectral beam shifts of the X-ray tube, beam hardening from the adjacent tissues, and scatter and, also, to a great number of different processor factors as to how the film is developed exactly.

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That leaves us with the modern methods that are used for both densitometry of the skeleton for patients with osteoporosis and also for evaluation of fracture healing.

There are basically three of those that are in widespread clinical use. They include quantitative computed tomography, single-photon absorptiometry and dual-photon absorptiometry which are radioisotope techniques, and the newest of these which is called dual-energy X-ray absorptiometry or DEXA.

All of these methods are similar in that they measure attenuation of an X-ray beam and compare it to some sort of a known standard. And they all have high correlations from one technical matter the other.

QCT and SPA have been used to evaluate fracture healing and are said to have higher correlation with the gap properties of the tissue than does DEXA. But that was done when DEXA was still very new so the data is about eight years old now. That is almost certainly not correct because DEXA, in all other respects, exactly mirrors the findings on dual-photon absorptiometry.

So, given that, we think that these tools probably all have similar data, and dual-photon studies probably are in the process of being discarded because of technical shortcomings compared to DEXA and the equivalence of the

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data.

[Slides.]

So, now we are down to two. We have quantitative CT and DEXA. Now, quantitative CT is the most sensitive method that we have for detection of cancellous or trabecular bone loss. So, therefore, for early changes of osteoporosis, this is the most sensitive method.

It is sensitive because it is a true-volume method which is to say that a CT section has a thickness, a precise thickness, and, also, a precise dimension and it is possible to evaluate purely cancellous bone and exclude cortical bone.

Because of this property, it has been used in the evaluation of these types of patients with the bone void fillers to show that there can be considerable variation in the pre-implant bone void filler. This has been shown by quantitative CT, again, because of its volumetric capabilities.

[Slides.]

This is what it looks like when you do it in a real patient. This is a typical osteoporosis application. We have the patient lying on a densitometry phantom. The scan sections are programmed by the computer to have a precise localization in space. And then you sample the

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region of the skeleton that you are interested in by this type of a volume and you compare it to the known attenuation in the phantom.

Basically, since this is a known linear relationship, the density and the attenuation are known to be linearly related. Therefore, a simple linear regression can tell you what the equivalent density of the bone is.

This method is very good, as I said, for trabecular bone in the spine. However, it has not been successful in applications to the appendicular skeleton in part because of difficulties in defining this region of interest which appears simple but, in fact, is not.

But that is not to say that CT, per se, can be very useful in evaluation of these bone fillers because it is an excellent method of obtaining thin two- or three-dimensional examinations of thick body parts just where plane film is at its worst.

So, for example, Dr. Lane mentioned the difficulty of the allograft bone evaluation healing and he said that I might need sunglasses to do it. But, in this case, with the latest versions of the CT software, the metal suppression artifact has been greatly improved and it is possible to appreciate, not only the position of the graft but, also, the relative incorporation or lack thereof from the CT

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section.

So I would keep that in mind as an available tool. It has not been much used for this purpose in the literature.

[Slides.]

As I said, the SPA, the dual-photon or single-photon methods are radioisotope methods. They give absolutely equivalent data to DEXA. They are old. They are out of date. And so, probably, these should not be used for any types of ongoing trials.

DEXA, though, is a viable alternative. This uses a dual-energy X-ray beam. It is now the most prevalent method in the world for evaluation of osteoporosis, particularly in Europe, interestingly enough, but also in the United States.

It has, as I said, been shown to be related to the properties of the gap tissue in fracture, the density as measured by this method. It can be used in proximity to metal and it has been shown that it is sensitive to very small gaps--in other words, the spatial resolution is sufficient to detect a gap in the order of 1 millimeter or less.

But, the other thing I would caution you about is that the density, as measured by DEXA, is related to

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strength but not directly. So, for example, there have been a number of patients that have been treated with tibial plates and then the plate has been removed. In fact, it has been shown that even though we know that the mechanical strength in the immediate plate-removal period is diminished, nonetheless, on the DEXA scans, the density was up and over the period of a year, the density returned to normal so that there is not a simple one-to-one relationship between density and strength.

In fact, recent data suggest that in the process of fracture healing, density, as measured by these techniques, rises rapidly in the initial period and is accompanied by stiffness but does not accurately track with ultimate breaking strength. So stiffness, in the early phases, and density have a close correlation but not ultimate breaking strength, unfortunately.

DEXA has been used widely to evaluate bone densities following total hip repairs. It can be done in close proximity to metal. It is said to be sensitive to changes of less than a tenth of a gram per cm² of tissue, It is a planar measurement.

[Slides.]

This is what it looks like. A DEXA device is a dedicated machine. There are about four different vendors

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that produce this kind of a scanner. It is a conventional X-ray tube which is usually modified in some way. In this instance, it has been used to scan the hip and can be used to measure the projected planar density of any region that you can either mathematically or subjectively define.

So it is a pretty robust technique.

[Slides.]

So much for density. A lot of other imaging studies have been directed at the evaluation of perfusion of these implants. I would say that perfusion scanning is interesting as a measure of biological incorporation at some level but it is certainly not equivalent to incorporation.

An implant can be perfused and yet not incorporated. Perfusion has virtually nothing to do with ultimate breaking strength. There are a number of nuclear-medicine techniques that have been used. One can use the conventional bone-seeking agents that are used for bone scanning. You can either get delayed images which show the ultimate deposition of the radioisotope in the bone or you can get the so-called blood-pool phase which is done immediately after the injection to look for a vascularity.

The blood-pool images can be done also with conventional blood-pool agents such as thallium that is used for myocardial perfusion studies. It really doesn't make

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any difference.

[Slides.]

This is a conventional bone scan done in the static phase to evaluate the incorporation of this, in this case, vascularized fibular autograft. So you can see on the AP radiograph that this patient has sustained a massive femoral allograft. The junction site is here. The allograft has fractured and this fibula has been implanted to bridge the fracture.

On the radioisotope bone scan, one sees, from the anterior projection, the cold defect which is due to the allograft and then the uptake which is in the vascularized fibula seen right in the middle. On the lateral image, you can see the same thing. Here is the vascularized graft along the anterior surface of the femur and the cold distal femur is the allograft.

But I also will point out that along the margins of the allograft, there is some uptake which, undoubtedly, represents early--well, maybe not early but some--degree of perfusion of the largely otherwise avascular allograft.

So this type of technique is quite widely available.

[Slide.]

The other thing is that, depending on the anatomic

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resolution that is required, conventional scanning can be combined with a technique called SPECT imaging, which is single-photon emission computed tomography, which increases the anatomic specificity and, also, the sensitivity of the technique but basically gives the same data.

There was also another technique which is available in the nuclear-medicine area called PET imaging. PET imaging is a fantastic technique, really. It uses antimatter. It uses positrons to look for annihilation radiation when positrons collide with matter. The annihilation radiation allows one to calculate the location of the source of the isotope.

The most common PET image agent is called FDG, or fluorodeoxyglucose, which is an agent that gets trapped in the Krebs cycle and, therefore, is a marker for glycolysis. It has a very large number of different applications but, as far as I know, there is no current data that would suggest that it is of any use for fracture healing. Maybe it will be sooner or later, but I doubt it is going to be a major one in view of its cost and complexity.

[Slide.]

That leaves us with magnetic resonance imaging which seems to be able to do absolutely everything these days. Magnetic resonance imaging, as a tool for evaluation

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of perfusion, does require the use of intravenous gadolinium, and the perfusion is evaluated by the changes in the signal intensity which is seen on T1-weighted images. The great value of it is that it is a three-dimensional technique with a great deal of anatomic resolution.

[Slides.]

Here, for example, is an allograft, a radiograph, which was taken synchronously with this axial PET image. Now, everything that is white on this image has had its T1 decreased by the administration of intravenous gadolinium. One can see that on the surface of what appears to be a completely unremarkable allograft, one sees a tremendous amount of vascular ingrowth coming from the outside in.

So all this represents viable vascular tissue, not necessarily bone. It is also impossible to imagine how this type of anatomic specificity could be gotten out of a nuclear-medicine technique, I think.

[Slides.]

Another finding in another case shows a similar thing. This is a plane film which was taken at the same time that this MR was done. One can see, perhaps, a very slight degree of soft-tissue swelling over the medial aspect of the femur but, on the MR, one sees this massive synovial hypertrophy arising from the knee and, also, this cuff of

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vascular ingrowth into the cortical bone of the allograft femur.

Also notice the very striking abnormal marrow of the allograft compared to the patient's own femur.

So perfusion scanning, using magnetic resonance, is something that probably is available in a lot of places and can be done if perfusion is the objective.

[Slides.]

The last topic I want to point out, in talking about imaging, is that whatever imaging technique is going to be selected, it should be aimed at the detectability of potential problems that one might anticipate. We have talked about non-union, delayed union and loss of alignment. Infection, of course, is always a problem, and fracture. So all of these things can be handled by plane film.

Tumor recurrence, to some extent, can be handled by plane film. Radiopaque implants usually will be sharply demarcated from tumor recurrence which tends to be lytic on plane films and migration of the implant as well might tend to be handled by plane film but might require CT, if it is in the axial skeleton.

Resorption of the implant would do better with CT, perhaps, as I will show you in a minute. And the foreign-body reaction which is quite important may also

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require either CT or magnetic resonance.

One of the things which I think is probable is that, as we go forward with more and more bone void fillers, we are going to encounter more and more foreign-body reactions. I see this quite commonly in my practice. It is virtually a daily event because of the large number of total hip-joint patients we see.

But particulate debris of almost any type can cause adverse consequences. It can cause a foreign-body reaction within bone and it can also cause a synovitis if it gets into joints. It is manifest, usually, by a progressive osteolysis which can be massive. And, as I say, it is most often seen following joint replacement and it has recently been shown to be sensitive to additives that are put into the bone void filler.

So, for example, barium appears to increase the tendency of methylmethacrylate particles to cause granulomatous foreign-body response.

[Slides.]

It can be very subtle. This is an example here. On the left-hand screen, you see a plane film of this patient with a bilateral hip replacement. On the right-hand screen, we see a reformatted coronal CT image which shows a massive area of osteolysis in the posterior ischium just

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behind the acetabular cup.

You can see the margins of this lysis extending down to the ischium, virtually invisible on the radiograph. It is present. If you look carefully, you can see it, but it is not at all impressive compared to what the CT is showing us is massive resorption.

[Slides.]

It isn't always necessary to do CT. Sometimes, the foreign-body reaction can be so spectacular that you don't even need to image the patient at all. As, for example, here, is a patient who went from this condition to this condition in a period of less than a year.

So this is a very massive foreign-body response to particles probably of polyethylene. But it could be methylmethacrylate. It could be silicone. And I think it could be bone void fillers.

[Slides.]

Here is a silicone example of a similar type of thing. This is a silicone implant of the lunate bone that was done in '75. You see that the silicone, itself, is intact, that the lunate looks like a normal lunate, perhaps a little bit large for this wrist but normal in other respects.

Then, six years later, you can see that the

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implant has now collapsed spewing particles of silicone into the synovial tissues of the wrist and leading to an erosive synovitis which has caused all of these erosions, multiple cyst-like lesions and, in fact, causing adenopathy in the forearm and axilla as well from the silicone particles, a very well-known phenomenon with silicone implants, particularly breast implants.

[Slide.]

So, what are the conclusions. I guess the conclusions that I would suggest are that imaging has a lot of different roles. It can be used for a lot of different things. But if I want to leave one message it is that it is not a standard black box.

I think it would be a mistake not to pay very careful attention both to the study design and looking for double-blindedness, in particular, and the expertise in respect to imaging on the part of the people who design the study because it is not a simple matter of turning something in to the radiologist, having him put on his sun glasses and saying yes or no.

There is a lot of judgment here and a lot of room for error.

So, thank you very much.

DR. HANLEY: Thank you.

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MS. NASHMAN: At this time, I would like to thank all of our guest speakers, Drs. Friedlaender, Yaszemski, Lane and Rosenthal. We at the FDA truly appreciate the information you have just provided and shared with us. It think it serves as an excellent backdrop for the discussion that we are going to have during the remainder of the afternoon.

At this time, I would like to present Ms. Nadine Sloane who is going to provide us with some pre-lunch food for thought, the questions that are going to be discussed after lunch.

Nadine?

Presentation of Questions

MS. SLOANE: Good morning. I would like to start reading the questions that we are going to discuss this afternoon.

[Slide.]

The first question relates to mechanical properties and preclinical testing. There is a lot on this slide. I am not going to, necessarily, read it all. But, what would you consider to be important mechanical properties for a bone void filler and what preclinical tests would be helpful for short- and long-term assessment.

In answering this question, please consider the

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following: mechanical loading variability associated with different anatomical sites and types of bone; for example, metaphyseal and diaphyseal, cortical/cancellous, spin/long bone and different fracture types; for example, complex versus simple fractures and differences between traumatic fracture defects and defects resulting from resection of tumors. Also consider variations in defect size.

In addition, we ask that you consider the resorption rate of the material taking into account the time-dependent load sharing with internal fixation and long-term mechanical requirements after fixation is removed, especially for a slowly resorbing material.

We also ask that you consider changes in the material resulting from mixing it with autogenous bone, an osteoinductive agent, which would alter the material's inherent properties and potentially affect long-term composite strength as the osteoinductive process modulates the rate of bone resorption and formation.

The second question relates to the study design. First, how should differences in anatomical site and indications for use be addressed in the study design. For example, consider potential differences among studies for the treatment of fracture defects, defects resulting from resection of tumors or for filling the bone-graft harvest

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site, spine fusion, et cetera.

Are there specific indications or anatomical sites for which it would be appropriate to extrapolate data from to another. Also, what length of follow up is necessary, keeping in mind differences in resorption rate, defect size and the location.

The third question relates to imaging studies. First, what imaging methods are appropriate for the assessment of material fracture and migration. Also, which radiographic criteria--for example, cortical bridging, maintenance of fracture reduction, do you believe to be the most meaningful for evaluating device effectiveness keeping in mind the radiopacity of the material. Also, to what degree can radiographic data be expected to correlate with clinical outcome.

Our fourth and final question concerns clinical effectiveness measures. First, what clinical endpoints and assessment tools are appropriate to evaluate clinical utility and what are the appropriate success criteria for this product considering that there is an inherent benefit of bone void fillers compared to autograft in that second surgical site is not required.

So these are the questions which we are proposing for discussion this afternoon. Some of the previous

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speakers have already touched upon some of these, but we are looking forward to the panel's input.

I would like to thank the panel for their participation in today's meeting.

Thank you.

DR. HANLEY: Thank you.

I think what we will do at this time, if there is no objection, is break. Then we will come back at quarter of 1:00 and do our discussion and our questions.

[Whereupon, at 11:51 a.m., the proceedings were recessed, to be resumed at 12:45 p.m.]

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

[12:50 p.m.]

DR. HANLEY: Let's begin with the afternoon session. I think we had an excellent series of presentations this morning shedding light on what is involved in the design and study of what are called bone void fillers.

Myself, I felt quite comfortable with this. Many of us in the orthopedic community have had extensive experience with these things over the past two decades, so it doesn't seem as foreign or as difficult, at least to my view, as some of the other things we face on a routine basis.

So I think the speakers have put things into perspective very nicely and this will form the foundation for which we have our discussion and address the questions which the FDA has put to us.

I would like, at this time, to open up the floor for panel discussion concerning the issues discussed today in the context of the questions posed. We will consider the questions specifically after this.

Panel Discussion

DR. MILLER: I would like to commend the speakers for the excellence of their presentations today. I would

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like to recommend to our panel that we recommend to the FDA that we use their materials as a point of departure for the creation of a guidance document in the design of clinical trials for the investigation of the effectiveness and safety of bone void fillers and use that document and that material as a point of structuring that document.

DR. HANLEY: Thank you.

DR. GREENWALD: Thank you. I would like to also compliment the speakers this morning. I found that to be a really informative learning experience. It is certain to give the FDA the kind of information, direct information, I think they were looking for.

I would like to mirror what Dr. Miller has said that I think one of the endpoints of our discussions today should be contributory to the development of a guidance document on bone void fillers that had the purpose of serving both the Food and Drug Administration and their ability to assess incoming devices which are probably going to be numerous both in types and shapes and applications. and also, to serve as a guidance to manufacturers who are petitioning for the approval of such devices.

I think probably I would like to direct a few remarks towards what I would like to see develop into this guidance document, a paradigm for bone void fillers. How

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are they going to be assessed? We heard that this morning. From my own perspective, I certainly would think that the definition of a bone void filler can take on many shapes.

We heard this morning, certainly, about the potential of allograft, autograft, xenograft, synthetic materials of a ceramic or polymer nature. I would also like to add to that that porous metal also represents a potential bone void filler.

I would also like to point out that the definition of how you evaluate these things, both from a laboratory perspective and both a preclinical venue and a clinical venue is going to, I think, rely very heavily on just where they intend to be used in the body, in the skeletal system.

We can talk in terms, as it was this morning, of cavitory defects, closed and open. We can talk about segmental bone replacements or, for that matter, defects in bone all of which define different mechanically loaded environments all of which will define criteria that have to be substantiated from a mechanical perspective as well as a biological perspective in in vivo use.

I think that it is important to recognize--and it was laid out very well this morning, I think, in terms of the various areas of the skeletal system where fillers can be utilized.

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I think it is important along the lines of mechanical evaluation--this is not answering the questions but just giving you some thoughts about it--that the morphology of a particular structure--many structures that will fill the bill of bone void fillers may be isotropic in their shape and in their dimensions and behavior.

Others may, in fact, be anisotropic. And the way in which they are used in the body becomes highly defined. I think it is important to identify mechanical tests which can be done from the get-go. They certainly were mentioned this morning, certainly compression, certainly tension, torsion, stiffness and, also, the fatigue behavior of these virgin materials.

But I think it is also very important to bear in mind that these behavioral characteristics, physical behavior characteristics, are going to change in the in vivo environment, particularly if the facilitating corporation, through vascular incursion and either substitution or some form of biological, be it fibrous or bone tissue, to take up the volume.

And so there properties, particularly if they are resorption in nature, are going to have to be established at different time intervals bearing in mind that if they are utilized in a fracture environment that, as time diminishes,

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you expect that the healing bone will take up more and more of the load.

Otherwise, the implant, itself, may, indeed, break, as has been our experience over the years.

I think it is important to recognize that in the evaluation of these materials, you have to evaluate them given the potential environment they find themselves in which may not just be loading. It may also be influenced by radiative chemotherapies as was pointed out to us this morning.

I think it is important to recognize that once these environments, in fact, have been defined, the materials that are chosen, indeed, have to then be exposed to mechanical testing preclinically in those environments because I think you can learn an awful lot about the success and failure of a material a priori, before clinical implantation

Perhaps I could stop there and others can chime in.

DR. HANLEY: Thank you. Other comments?

DR. BOYAN: I would like to support what everybody has said but I would like to add a few things. As I heard the discussion this morning, I heard a heavy reliance on the concept, or we keep trying to go back to the concept, that

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these materials, the bone void fillers or bone graft substitutes are--that the field is moving forward, it is moving away from those kinds of materials to the kinds of things that Dr. Lane talked about and Dr. Yaszemski referred to which are materials that were never intended to be weight-bearing or load-sharing.

In fact, they are intended to remove themselves from the system either through chemical degradation or through biological degradation over the course of time that the bone is healing. The ultimate goal would be to get these materials as the bone heals.

So, as we make recommendations to fracture about what we would like to see happen, I think we need to include, in our wording, that these materials are the future materials and that the criteria need to be thought of in that context.

To further what you are saying, Seth, we need to think of testing them mechanically under relevant conditions. These materials are going to be doing their job at physiological pH and at physiological temperatures and in an aqueous environment. So much of the testing that has gone on until now has been done on dry materials at room temperature and not, necessarily--the mechanical properties that they exhibit under those conditions may be very

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different from what they will actually exhibit when they are put into bone and expected to do their job in bone.

In this context, I really mean materials that are going to be biodegradable or are chemically going to degrade but in a biological setting.

One last comment I would like to make about how we go about assessing the value of a material. Dr. Lane made a beautiful schema of starting with rats or rodents going on to a higher animal, doing limited studies in monkeys and then going on to the human.

I would like to support that concept, but add that rats are not necessarily a bad place to start. In fact, as we get more and more understanding of higher animals, it is harder and harder to justify doing experiments where the questions could be handled very easily using rats or mice.

There are many things of relevance to orthopedics or, since this is a device panel, not necessarily orthopedics but to plastic and reconstructive surgery or in dentistry where rat models, in the cranium, are perfectly valid ways to betatest a product at the beginning.

Rats don't always heal. They heal more easily, certainly, than higher animals but they don't always heal completely. We can learn a lot from what rat bone does in the presence of a material that would save us an awful lot

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of higher animal studies that would not have to be done needlessly.

So I suggest that we not discount the rat. The Ph.D.s that you know are wonderful rat doctors. I think it is the first place to start and really exploit the rat before moving on.

DR. HANLEY: They are the only rat doctors.

DR. BOYAN: That is an R.D. for rat doctor.

DR. HANLEY: Thank you.

Other comments from the panel? I would like to bring up a few issues. One is sites. Do different sites warrant different criteria for design, different tests and different clinical study. Dr. Lane has suggested to us that a reasonable way of dividing these sites is metaphyseal, diaphyseal, arthrodesis, spine, anterior versus posterior and arthroplasty as reasonable, clinically relevant, site-specific, definitions.

Obviously, it is impossible to have one for every bone in the body which this might be used in. Is this a reasonable designation or should we just have what has assumed to exist in the past; they are all the same, test them all the same, use them anywhere you want.

DR. GREENWALD: Well, they are not all the same. I think Dr. Lane's commentary is very well positioned. I

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think that one has to determine the mechanical environments in first instance that these devices are likely to see.

Some may be excellent in compression but terrible in tension. Materials, by themselves, will sort themselves out as to just where in the skeletal tree they are going to find applicability. So I think, actually, his scheme is pretty good. I think that ought to be incorporated.

DR. FRIEDLAENDER: I would support that. I think that Dr. Lane's approach was a rational balance between lumping and splitting. We certainly don't need to consider the right and the left femur any different. We don't need to consider, I think, in most cases, the femur different from the tibia. I think that that approach, as outlined, is driven by good reason. I agree with it.

We also have to address, at some point, I suppose, the difference between a gap model and a fracture model.

DR. HANLEY: Yes; I think that is true. I think this is the time to do it although, to me, I think it would be easy to suggest that the diaphyseal model, in essence, is a gap model or materials used there would have to meet the criteria for your gap model.

What do you think?

DR. FRIEDLAENDER: I would agree with that comment as well. I think, in a more philosophic sense, what we are

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really in need of is defining the characteristics of materials and approaches and then using clinical judgment to match them to circumstances that make sense.

I don't believe that every approach needs to meet a predefined threshold by any parameter. It is more important to know what it can do and what it won't do and how those characteristics change over time and then match them to the appropriate clinical circumstances.

DR. MAYOR: I am sort of trying to search for the best way we can contribute to FDA's efforts in relationship to what Seth is suggesting. I think it is entirely appropriate that eventually what needs to come out of this is a guidance document.

But I wonder about two things. One is Dr. Boyan's suggestion that the trend is away from structural design, but I think that that is probably too limiting. My sense is that what the FDA needs to do is to make room for sponsors who want approval for a non-mechanical device which is more biological and stimulatory and, at the same time, make room for other sponsors who want a device which not only takes up space in the musculoskeletal system but, also, bears load or could bear load, either temporarily or persistently, depending on the how the thing is designed.

I think we are going to see, as this whole process

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evolves, both things happening.

The other thing that occurs to me has to do with what we just discussed this morning, and that has to do with how the FDA uses the panel, both to accomplish the process of crafting a guidance document and in the process of looking at individual sponsor's proposals early in the game so that they can be brought to fruition more efficiently, more economically and with less likelihood of back-and-forth moving-target concerns on the part of the sponsor.

I think the final thing that I am concerned about in relationship to the evaluation technique that is used is the real necessity to carefully examine the instruments that are available so that the data we collect includes a significant body of patient-centered information.

The outcomes that patients enjoy have already demonstrated to be quite distinct from the outcomes that physicians perceive the patients are enjoying.

DR. HANLEY: Or that our so-called objective tests or images reveal. Well said. So I think there is a meshing there between the functional, structural demands and the sites that can be worked together.

DR. TRIPPEL: Before we leave the subject of site specificity, I have a question for the panel. It has to do with whether we really need to impose any constraints on the

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manufacturers with respect to the biomechanical characteristics of their product and where they put it.

If you have a material that has no structural capability, you could still put it in a site which has enormous loads going across it if you are providing some other means of stability.

If you have a femoral rod or a tibial plate and you are putting in a bone void filler to try and get rid of the void, you don't need that filler to provide any mechanical support. On the other hand, if you are putting a device in a spine and you don't have any ancillary fixation at all, obviously it is going to have a very different role to play.

So I would just inquire whether we shouldn't be couching this recommendation in the context of ancillary fixation.

DR. GREENWALD: Again, that is a good fulfilling comment. If you look at the statements of safety and efficacy which were included in the panel documentation that was given to us, you recognize that both the PMAs were approved on the understanding that they must be used conjunctively with some form--in one instance, it was an internal and/or external fixation and at the other end with an internal fixation.

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So there was a recognition made on the part of the panel who evaluated them at the time that these materials, in and of themselves, wouldn't have been structurally capable, at some level, of carrying the imposed external environmental.

So that is a very good and important point and it should be included, that adjunctive means may well be necessary to establish the efficacy of these, in fact, bone fillers.

DR. HANLEY: I thought that was rather implicit, but it is nice to revisit it.

Let's address the issues of controls. This is always a sticky point in all of our discussions. I have yet to see come to our panel what I thought were adequate controls from a scientific sense. What kinds of controls should exist for clinical studies done on bone void fillers?

DR. BOYAN: I think that Dr. Lane stated it pretty clearly, that the best control is autologous bone graft as a positive control, and a negative control with nothing. For an animal study, I think that is intuitively obvious that for a decent study, there has to be a positive control and a negative control and those are the two right positive and negative controls.

However, as we get to higher-level animals, I

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think that if a research group has got a reasonable amount of experience, perhaps with the negative control, no bone graft, they could rely on that if, in their hands, there is sufficient data to say that the negative control goes on to non-union or whatever the negative outcome. For animals to lose their lives for science needlessly does not make sense.

By the same token in humans, I am sure that, from a clinical point of view, it would be difficult to justify no therapy or no graft in some situations. Maybe there are instances where no graft would be an okay clinical approach, but there has to be a positive and a negative somewhere in the literature or somewhere in the study to make it a scientifically valid study.

DR. HANLEY: Right. I think we could get quite specific on that. There are situations where no graft would be the standard of care, would be an acceptable control, and others where it is not. Obviously, in the area of spine fusion, for instance, no graft is not acceptable but standard treatment as autologous bone graft and could serve as a nice control.

In the acute treatment of a tibia fracture, standard of care is internal fixation, no graft. That could serve as a control against internal fixation with synthetic bone void filler, synthetic filler, synthetic graft,

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whatever you want.

So we will, I think, have to advise them to use their judgment on the clinical situation. I think it is not tremendously difficult to figure out where it is appropriate and where not. The point is you need good, standardized controls which reflect either the natural history of the disease or a standard form of therapy currently in practice.

DR. FRIEDLAENDER: Just a point. The way we use these terms may turn out to be more important later on than currently. The use of the word "control" to me implies an approach to validate the method, a positive and a negative. On the other hand, often what we are looking for is a comparison between two alternatives and whether or not there is equivalency or superiority of one versus the other.

In other areas of experimental design, you really are not allowed to use the control as the alternative. You have to separate out the concept of control and comparisons.

Do you understand? Am I--

DR. HANLEY: I understand what you are saying but I think, in a clinical series, we have evolved away from that to have "control," meaning either no treatment or comparison treatment. I understand. As long as we get the definitions right, that is the important thing.

DR. FRIEDLAENDER: My point is really one of

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definitional clarity. That, in my mind, helps facilitate the discussion. There are examples where the comparison of standard treatment is not based on good science. Or there may be some difficulties in interpretation.

As an example, I would point to the healing of a fresh fracture, for example. It is not uncommon, as clinical practice, to use bone graft in association with an acute fracture. It is not scientifically clear that that bone graft contributes to the end result or, if so, how frequently.

Most fractures heal, especially in our friend the rat, for example. It is very uncommon for a rat with a broken bone to meet an orthopedic surgeon. It does happen, but it is uncommon. So sometimes the control autograft satisfies our need to compare with a standard accepted methodology.

But, in fact, it may be that neither the autograft nor the new treatment are required for the beneficial result that we are seeing.

DR. HANLEY: Okay. I think we have figured that one out. Let's move on. I would like to bring up the issue of measurement of success or failure or somewhere in between and just a broad discussion of the clinical parameters, as Dr. Mayor has said, the patient-oriented parameters or

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outcome, as viewed from their eyes, and a little discussion of these images that we use that we sometimes think may be helpful.

DR. BOYAN: I would like to address the images. I think that it is a very important point that has been raised here and one that has application to preclinical studies as well as clinical studies. Radiographs really are the one longitudinal measure of the success of a treatment as the animal is going through its healing process or as the patient goes through his or her healing process.

You can monitor that with a non-invasive imaging technique where you can't monitor it by other measures. What I would like to suggest is that we put forth to the FDA that they consider in their guidance document that in preclinical studies that, at the time of euthanasia of the animals, where the animals are actually going to be euthanized in the study, that specimen radiographs be made using a jig so that there is an alignment, that they can actually go from study to study and within a study and use some sort of step wedge or quantitative measurement.

I think that our outside expert has made clear that there are much, much better technologies now for insuring this, that I think there is an equal number of really wonderful scientists that may not have access to that

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technology who could bring quantitation into what they are doing with some very simple additions to the studies that they do.

Then, for the human studies, what I see clinicians doing, and I am not one, but this is the thing that I always am amazed with, is no matter what other data I show a clinician, the clinician relies on the radiograph.

So I think we need to view the image that they see as one of the most important assessments that they are going to use in determining whether or not a treatment is efficacious.

DR. HANLEY: While we are on images, let's talk some specifics about images. My take from the presentation and, also, my clinical opinion is that plane films have a role, that QCT and DEXA are sometimes useful but we haven't quite figured out where their real role is.

We get interesting information. We are not sure it correlates sometimes. MRI is not quite there for bone yet except in certain centers where somebody is playing around with it for that specific purpose. But it certainly isn't the standard.

Maybe I am off. That is my view. I am uncertain as to what should be mandated or suggested in clinical trials in humans with regard to the images. I would say it

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is at least plane film. But what else? Comments?

DR. MAYOR: I would agree that the plane film is probably the place that everybody is going to go. We have 100 years of technological experience and each clinician has the lifetime of his or her own experience looking at not just a single radiography but a sequence of radiographs starting at time zero and progressing from there.

That is a very sensitive source of interpretation about how the biology of the patient or even the animal is responding. We did a study some time ago which suggested that even as small as 15 degrees of rotational realignment of a long bone changes the density measurement so profoundly that you can't use them.

We have also heard that density does not correlate with mechanics. So I don't know that these elaborate and very precise measures of density are really going to get us anywhere that we need to go.

DR. HANLEY: Right. As before it might have been mentioned, oftentimes the density is inversely related to the mechanical properties of the thing we are measuring, witness osteonecrosis, witness, I presume, the ceramic implant that was in those wrists.

So it really is difficult to correlate that. It doesn't mean we shouldn't use that. Like QCT and DEXA have

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a role somewhere, but it is difficult to define in these types of studies.

DR. RANGASWAMY: If you are using radiographs or even MRI, obviously one assumes that whoever is doing the study is going to standardize these methods and also evaluate right from the beginning for interobserver and intraobserver error because there is going to be a lot of that. It is a visual image that they are going to read and I think that is something that should be built in right from the beginning and then not look at the study two years from now and say, "Gee; you didn't standardize it. It is really useless. You have got to go back and do it again."

So I think that is something they should look at.

DR. HANLEY: Further comments?

DR. FRIEDLAENDER: I agree that whatever method is used should be reproducible. I think it is up to the investigator to demonstrate that it is reproducible, firstly. Second, I think we are all very comfortable with standard radiographs. Once you move beyond standard radiographs, the technology ought to answer the question being posed.

I think as the question changes, the use of technology will have to change as well.

DR. LANE: I think that there are two

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circumstances. One is the preclinical trial and the other is the clinical trial. When you go to the preclinical trial, you have the advantage--as you work out your methodology, you can confirm that your radiographic methodology does coexist and it is an agreement with mechanical testing, I think either the White Panjabi or one of those other methodologies which are out there.

I think that you also have the advantage in a preclinical trial to use a fixation device which is not acceptable for clinical treatment such as external fixator or something that will not interfere with the radiographs.

So one of the challenges is that you think, if the panel feels, that radiographs are your best tool for sequential study in the same animal, the experimenter can use a fixator or a device technique which will not compromise the X-rays.

You are either using different kinds of metals or some other methodology which will not interfere with that particular process. So I think that is one advantage.

The other thing is that does the panel want to move forward on the areas like Ken Wright and Goodship and these other people who actually have devices built onto their fixators which can then look at the mechanical three-dimensional array of that fracture. The English have

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certainly been very advanced in that technique. Again, it would have to be done in a preclinical--even though Ken Wright, I must admit, uses this in patients as a method to confirm it.

So the bottom lines would be; one, make the experimental model such that it is user-friendly for the radiograph if the radiograph is our best tool. two, confirm that the radiograph agrees with the mechanical data; and, three, in preclinical trials use devices which allow continuous mechanical evaluations.

DR. HANLEY: Thank you.

DR. TOMFORD: I would agree that the imaging studies are extremely important. However, I think that they cannot be used alone to judge healing, incorporation, other parameters. I have seen too many allografts that I thought were healed by radiographic analysis that turned out to be, upon exploration, non-united.

So I think there is still a role for other types of assessment and I would say the radiographs have to be put into the panoply of evaluations.

DR. HANLEY: That brings up the other issues to discuss, the measures of pain and functional outcome, both from the perspective of the treator and the patient or the rat or whoever it is.

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DR. NELSON: I think one of the things that we should have as an overall caveat is that any of these tests should have a demonstrated reliability, validity and, in some way, relate to the patient population being studied in terms of the age, gender, race, language, et cetera.

I would hope that we would consider maybe three broad areas. One would be health-related quality of life, some kind of multidimensional issue, a broad-based patient satisfaction kind of questionnaire, not just a univariate kind of question, are you happy or not happy, that kind of thing, but rather a broad-based patient satisfaction questionnaire.

And then, when they do measure some of the measurements of impairment, some standardized forms of impairment, again going back to this overall criteria that the reliability, validity, has been demonstrated by prior studies and they can relate it, again, to the patient population, et cetera.

DR. HANLEY: Very good. We always face this issue and, after many discussions, that is a nice summary of what we really should be measuring and, when we measure it, we ought to be able to justify it, that the measurement is valid.

DR. CLAUW: I agree with Dr. Nelson and I just

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wanted to expand on a couple of things. I think that, for some of these scenarios, I agree entirely that we need to use validated instruments. But I could imagine some of these studies where you might have to develop novel tools, in addition to these other instruments, to use.

For example, when you are trying to compare the discomfort associated with taking an allograft from the hip, and weigh that against what the success rate might be with the synthetic material where you don't need to do that procedure, there is no validated questionnaire that would in any way get at that construct.

I think that, in some settings, you are going to have to try to ask those kinds of questions in sort of a novel questionnaire. You would have to have the other questionnaires to, in part, validate that.

The other comment I would have, and this is more generic for the FDA in general for all kinds of studies with devices than it is specific to this one is that, given what has happened with things like silicone breast implants where no one ever dreamed, initially, that there would be a systemic problem, real or alleged, that occurred in conjunction with silicone breast implants.

My suggestion is that the FDA require, or at least strongly suggest, to manufacturers that when they are doing

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these kinds of trials, that they include some kind of questionnaire that looks at systemic symptoms, somatic symptoms, at the time a device is put in and follows that over a period of time.

If that were available with silicone breast implants, we wouldn't have had the problem with breast implants that we did have. The lack of data was really what fueled a lot of the problems with silicone breast implants, not commenting in any way on my own opinion about what happened with silicone breast implants.

I think that it is important, even though we might not feel as though there are any potential systemic complications from one of these devices, the same thing was thought 20 years ago with breast implants. Now, there are other medical devices where there are systemic illnesses being alleged or purported.

I think that if you require the manufacturers or at least suggest it for their own benefit that they collect that data, you might be ahead of the game a little bit.

DR. HANLEY: Thank you.

DR. NELSON: Just more of a question, Dr. Clauw. How would you separate out the iatrogenic effect, then, of these kinds of questions? Should I have this problem--if they are asking do you have this, this, this and this, how

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would you look at kind of separating out the possible iatrogenic effect of all of these questions.

DR. CLAUW: If you are using the same set of questions in both a treated group and a control group and you have picked your control group appropriately, then that shouldn't be an issue because, in most cases--and, once again, you get to this notion of what is a control, what is a comparison--but, in most cases, the comparison group will have received some type of treatment and so there won't be--the people that receive one treatment will think they are supposed to develop one set of symptoms whereas the people who receive a different treatment will think they are supposed to develop another set of symptoms.

In general, I think we can worry about the data afterwards and how you interpret it, but if you don't collect it, then you have a far bigger problem than how you interpret it.

DR. BOYAN: Along the lines of what you are saying, one of the things that did strike me as I looked through the information that we had to prereview before we came here, is the standards of our biological knowledge of materials and how bodies respond to them is orders of magnitude greater than it was at the time that the two currently approved, through PMA, products went through the

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system.

The terminology that may have been used then, bioactivity, benign, the whole series of terms that would have been used then, would not be used now. A lot of these issues will now be answered in preclinicals. Through extensive toxicology studies, there is much more awareness of other tissues in the body that might be affected, systemic effects, that were not of concern at the time that those two products were reviewed.

I think that many of the questions will be sifted out by the preclinical information and won't even need to be asked in the human trials.

DR. SILKAITIS: I just wanted to make a comment for the panel members to give a perspective of industries who have already done two PMAs for these types of products. These trials are exceeding difficult to conduct. There is wide patient variability. Part of that is because there is non-uniformity of the injury. The treatment methods; one is planing, one is rodding.

There are other systems that are used to fixate the bone. The quality of the patient is another issue that crops up in these clinical trials that always the patient that is injured is not from a reliable patient or that the doctor/patient relationship does not exist so that the

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follow up certainly becomes difficult when he is seeing a doctor that is not his own doctor.

The other gets into the number of patients that are available at a particular investigator site. We may need many, many investigator sites. That becomes a complication in the statistical analysis.

The other item is the fact that there are a wide variety of materials. We have ceramics that resorb, ceramics that don't resorb, and we have inductive proteins that disappear in a very short period of time.

All these factors create hurdles in conducting these clinical trials. And, with that, is the cost. The two trials that were done through the PMA took more than four years to complete and probably longer with the analyses that are there.

So these are not easy trials to conduct. The issues that have been presented here are certainly key issues.

DR. HANLEY: Thank you. I think we are ready for our questions.

Discussion of FDA Questions

MS. NASHMAN: During the process of going through the FDA's questions, I would just like to remind the panel that it is appropriate and fine and dandy to just ask our

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speakers any questions as they may apply. They are here for our benefit and it is best that we utilize their knowledge.

Thank you.

DR. HANLEY: The questions have been displayed previously. I will read the questions in order. We can go through them and comment upon the questions. Then I will attempt to summarize each.

Question No. 1; mechanical properties, preclinical testing. What would you consider to be important mechanical properties for a bone void filler and what preclinical test would be helpful for short-term and long-term assessment? In answering this question, consider the following: (a), mechanical loading variability associated with different anatomical sites, differences between cortical/cancellous bone, metaphysis/diaphysis, differences between spine and long bones, fracture type, et cetera, different types of fractures, tumor-resection defects, et cetera;

(b), material resorption rate, considering the material's time-dependent load sharing with internal fixation and long-term mechanical requirements after fixation is removed;

(c), changes in the material resulting from mixing with autogenous bone, altering the material's inherent properties and potentially affecting long-term composite

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strength as osteoinductive processes modulate the rate of bone resorption or deposition.

This is Question 1.

DR. GREENWALD: In some sense, just reiterating some of the comments I made, I think it is important, as you specify mechanical properties and mechanical loading, that it is going to be site specific. Not every type of bone void filler is going to be suitable for every aspect of the skeletal system.

I think it is fairly obvious that if we are talking about segmental bone replacement, structural strength becomes a very important parameter. Bending strength, compressive strength are factors that weigh very heavily in the durability of such.

Talking in terms of the tibia, it is quite obvious that compressive loading and loading under repetitive cyclic environments becomes very important. Again, I want to reiterate what I inferred which was reinforced by Dr. Boyan, we are, oftentimes, talking about singular materials becoming composite materials during the biological process.

When that happens, through a period of substitution, that material, itself, may become weaker rather than stronger and the reliance then becomes more--the reliance that exists for adjunctive fixation.

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I almost hesitate to give you a specific type of engineering test, but they are very, very standard in conduct. The question is to have some parameter that they must live up to in an in vivo environment recognizing that those properties will, indeed, change over time as the filler does its job.

DR. MARKOLF: I think that when we talk about the term "bone void filler," we have to see what the intended application is. We saw this morning a number of instances in which we had large cystic defects that the orthopedic surgeon felt more comfortable putting in the bone filler.

Does this have a mechanical role and is it expected that this bone filler may, then, eventually remodel with or without inductive agents into a more suitable load-bearing structure.

We can talk about bone void fillers for cortical holes or segmental defects, as Dr. Greenwald has said. Basically, we have to define what our remodeling expectations are for that filler. Is it just supposed to look pretty, or is it supposed to actually develop into something that will carry load.

In terms of preclinical testing, I think when we are talking about the osteoinductive agents, in particular, we have to go to animal models and then we have to make

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sure--basically, the rule of thumb here is that the type of mechanical test that you do is tailored to the individual application for the bone filler. That seems pretty much obvious.

When we are talking about animal models, we have to also consider the similarity of the defect site to a similar defect site in humans. In terms of the mechanical loading, does the bone that we are creating the defect in serve the same mechanical function as it does in the human and what is the blood supply to that area. Is the blood supply to that area similar to a human application?

In terms of the resorption rate of the degradable materials, basically we have a race between resorption rate and the rate of bone formation. That may not translate from an animal model into a human model. These rates may be different in the two species. Of course, we can do some in vitro degradation tests in saline and other simulated test in the laboratory, but that may not get to this issue of differential rates in the animal and human model.

Finally, when we are talking about the bone-inductive agents, we have to look at dose response for those agents. Again, that may not translate into the human application but animals are certainly, in terms of dose per body weight, a good place to start.

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So these are some of the factors that you have to indicate. The rule of thumb here is to tailor your test for the application.

DR. MAYOR: That gets down to what I would think would be the only workable approach in terms of a general perspective to bring to the process and that is to look very closely at what the sponsor's claims are for the function of this implant and then design the tests to see if, in fact, the sponsor's claims are likely to be fulfilled by virtue of the mechanical properties of the implants being promoted.

It also may be productive to maintain in mind a couple of broad categories of implant function that we see already well established in orthopedics. That has to do with the distinction between an orthotic application in which the implant is expected to function for a brief period of time until such time as that body part, in relationship to that implant, takes over, and then the implant has no further important mechanical function to serve, versus a prosthetic one in which you expect the implant to continue to function mechanically and importantly forever.

I think those distinctions may have some benefit to the FDA and to the sponsor.

DR. HANLEY: Keeping in mind that there is some desire here for an evolution from a prosthesis to an

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orthosis as time goes by.

I will try to summarize the comments that have been made so that we can put this in perspective. It is generally held that ascertaining and testing of the mechanical properties of these devices as they are presented is important, that they should be tested based upon their indications that are proposed for them.

We like the site definition in conjunction, site metaphysis, diaphysis, spine front, back, in conjunction with considerations of other uses such as bone defect substitute which then, obviously, you have a prosthetic desire for the implant versus a cancellous supplement or a non-structural supplementary bone void filler.

So the testing should be geared to those specific indications.

The testing also should take into consideration the diminution in mechanical properties over time that should be expected from some of these devices. That means physiologic or near-physiologic testing either in the laboratory simulated as best as possible in an aqueous environment over a period of time and the inclusion of animal models which are a better preliminary test of the in vivo situation.

It is the general feeling that there are animal

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models out there which could provide good information with regard to what is going to happen to these things over time if selected properly.

Any other comments?

DR. GREENWALD: The only other comment I would add, Dr. Hanley, and I said this at the beginning, that we are going to be dealing with materials now and into the future whose mechanical physical properties may be different in different directions. I am talking about anisotropic materials as opposed to isotropic materials.

I think that considerations like that weigh very, very important in the manner in which these devices are utilized in the body. The best biological example I can give you is allograft use in and around the acetabulum which, in some hands, has worked and, in other hands, has been a dismal experiment.

DR. HANLEY: This just gets to the point of specific--we are not here today to design a specific, mechanical test, but tailoring the specific mechanical tests initially and over a period of time to the specific material properties employed and the specific indications that are proposed.

DR. ROSENTHAL: I would like to make a very brief comment that has already been alluded to, but I think it is

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important that the regulatory stance that is proposed not stifle a short-term application because long-term criteria cannot be met. There are applications in bone void fillers for patients with a very short life expectancy; metastatic disease, painful vertebral collapses, and so on.

In those instances, considerations that might apply to a tibial plateau fracture don't apply. It is obvious, perhaps, but I don't want it to get lost here.

DR. TRIPPEL: It may be just being taken for granted but, in case it is not, I would like to comment for clarification that the biomechanical testing, I presume, would not just be of the bone void filler, itself. It would include interface mechanics because the way in which the material relates to the bone, either with chemical bond or bone ingrowth or fibrous tissue apposition, would make an enormous difference in how the body could be used.

DR. HANLEY: Very good.

DR. LANE: If the comparison, really, is to autogenous graft--that is basically what we have--or healing without graft, the minimum requirement might be that the construct, including the fixation and the device, was graded as compared to the autogenous comparison to which it is done.

It could even be worse than that at first, as long

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as the total construct was there. If it was bad in the first two weeks, it might not be very important because Barbara is talking about using things for carriers cells, et cetera. But as long as the total construct, the fixation plus the device, was comparable to the autogenous application throughout the course, including the removal of the device and long-term, that would also allow you to look at long-term remodeling and take care of things like allografts at seven years, five years.

So that is what your grading would be comparison against. And it would allow you to then look at the different locations and give you a standard.

DR. FRIEDLAENDER: Just a word of caution for the future when we talk about mixing with autogenous bone. There are very few circumstances where these materials and/or constructs are used in a non-orthotopic site which means, by definition, there are autogenous resources available. So it becomes qualitative rather than quantitative.

DR. HANLEY: Right. We would have to take that into consideration. I don't think we can consider every individual situation. We want to provide broad guidelines for this but I think all the points are important.

Question No. 2, study design. How should

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differences in anatomical site and indications be addressed in the study design? Are there specific indications or anatomical sites for which it would be appropriate to extrapolate data from one to another? (b), what length of follow up is necessary, keeping in mind differences in material resorption rate, data size and location.

Let's address the first one. We have had extensive discussion about this site issue. Do we need to elaborate more?

DR. BOYAN: I would like to elaborate to the extent, not to say that bone is bone because, site by site, bone isn't bone, but I don't think that we need to separate so completely the dental and oral and maxillofacial surgery applications from the orthopedic applications.

There is a tremendous body of data that is being generated in the oral and maxillofacial surgery arena that has direct application. Large segmental defects in jaw are not identical to large segmental defects in the radius, but they are not that different.

Defects in the condyle, while they are not identical to defects in the femoral condyle, they also share some similarities. So cross-referencing of data, I think, is certainly useful, specifically as it relates to safety issues. I think that a lot of the safety issues can be

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solved with just one or two demonstrations of safety. It doesn't need to be done completely in one arena and completely again in the other and then, with targeted trials for efficacy as opposed to having to do these tremendously large clinical trial for efficacy.

DR. MARKOLF: I think before we leave this, we were asked the question about different sites. Yes; I think you can extrapolate. For example, we saw this morning--some of the distal cystic lesions that we saw could be translated. Their bony architecture is similar and the loading function is similar. It is the same thing with mid-shaft defects in the tibia or the femur.

DR. HANLEY: We don't want to make a long list of different sites and different conditions but suggest to the FDA that there are various mechanical aspects of these three or four different things that were discussed, metaphysis and diaphysis. And the other things to consider are segmental bone defects where, obviously, the loading is going to be different in all planes, and some disease processes also.

We would suggest that we try to simplify this as much as possible but, at the same time, recognize the different applications and the different mechanical forces seen for these different applications.

DR. TOMFORD: I would just like to add that we

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heard this morning from two or three of the speakers about the role of the blood supply to the anatomical site. So when we are comparing or extrapolating data from one site to another, I do think we have to be careful about extrapolating, say, from the metaphysis to the diaphysis. The metaphysis of one long bone may be similar to the metaphysis of another long bone, but it may not be similar to the diaphysis of another long bone.

DR. HANLEY: I would agree with that and I think we have stated that, that in probably no instances would we extrapolate from a metaphyseal region to a diaphyseal region. But we might extrapolate from a metaphyseal-like region to another metaphyseal-like region.

DR. TRIPPEL: We were also asked to address the extrapolatability of indications. Certainly, some indications are more similar than others. A defect in bone that will not heal as a result of a tumor resection is, perhaps, somewhat similar to the defect that is left by trauma, but a critical size defect is not, necessarily, the same as an acute fracture which might require a different type of bone filler and might respond to that bone filler differently.

DR. HANLEY: Dr. Friedlaender brought that up today that a tumor patient is different from a trauma

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patient and a pediatric patient is different from an adult, an old, patient. Radiation, chemotherapy, all those things, have an influence.

So we need to match, as best as possible. We are not here to create a matching table today but rather to suggest that there are different types of hosts, different types of bones, different types of blood supplies without trying to micromanage everything, try to take those into consideration when considering a study design.

I would like to address the (b) part of this question which is the length of follow up necessary. Here, we are talking about human clinical studies. This is always an issue.

DR. RANGASWAMY: Would your length of follow up not depend upon the endpoint you want to look at? For instance, in a tumor patient, you don't want, necessarily, a two-year follow up of something which you might want for other devices. So I just wonder what endpoint you are looking at. If it is just healing and you have established that there is healing, that is the endpoint and that would be the duration of follow up.

Or you could establish that, if it doesn't seem to heal, how long will you continue to follow it and at what point will you decide it is a failure. So it would depend

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on the criteria that you establish for success and failure.

DR. HANLEY: I think we have already established that healing is not a satisfactory endpoint in any study that is presented, that we need patient outcome and clinical outcome and, in certain instances, imaging outcome.

So we have faced this before in our panel. Healing is not satisfactory. So I think we can get rid of that thing. The question is what is the appropriate period of clinical follow up. I think we can exclude from our discussion right now tumor patients and things like that. Let's talk about reconstructive bone surgery.

DR. TRIPPEL: I would agree with Dr. Rangaswamy that it depends on the indication. If you are looking at the effect of a bone filler on the stability of a distal radial fracture and your product is going to be asked to provide structural support for several years as it resorbs, then the duration of the fracture will need to be several years.

If you are going to be using a product that is made out of a synthetic polymer that is going to be gone in six months and replaced by bone in six months, then the duration of follow up should not logically be several years.

DR. HANLEY: Could I get another opinion on this?

DR. MAYOR: I think we have a pretty well

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established general agreement, part of it sponsored by organs like the JBJS, that an acceptable clinical cadre has to be followed for two years to get any realistic answers to relatively long-term, even though that is a very short-term in some circumstances.

But it is not realistic to require for criteria to approve a follow-up period of ten years regardless of what the question is because nobody is going to be able to come to market if you impose that burden on them.

So, realistically, while there may be circumstances when FDA might find it appropriate to shrink the follow up to a shorter period of time, you are still left with the safety issues that may have to be answered and those, I find it hard to believe, would be satisfactorily quelled with a three to six-month follow up duration.

DR. HANLEY: I think that summarizes extensive experience and discussions we have had concerning issues like this. I think that is a satisfactory answer. That would be viewed as the standard and there may be special situations where it is less or more.

But we are looking at the whole patient and the product together. Two years would be our standard.

DR. FRIEDLAENDER: I am having trouble putting a precise time on a process that varies so much from one

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indication to another and feel more comfortable talking about reasonable endpoints, a plateau of the response that you are trying to measure and stability of that response for some period of time.

I think that we have seen that there is a tremendous amount of investment in the concept of repair of non-unions, for example, where we have already collectively agreed that nine months is a reasonable follow up.

I think we have to be consistent about the way we approach results. I am very sympathetic to your point of view.

DR. HANLEY: I think that is a good addition to the question, that if we can measure in a validated fashion the state of the situation or individual or problem beforehand, and then, in a valid fashion, measure an outcome that goes up a slope and then peaks, if someone would be able to do that, then we could use that as valid scientific information.

We had discussed this yesterday, I believe. Barring that, and going back to our old-fashioned ways, we have to come up with some temporal ballpark figure and then make exceptions to it, I believe.

DR. MAYOR: Just a point of clarification, though, Gary. I think what Dr. Friedlaender has pointed out is not

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so much a criteria for evaluation of outcome but inclusion. The concern that existed in relationship to non-unions was is it a non-union or not. It isn't a non-union until it has been followed for six months and then hasn't changed for another three.

So that is at the other end of the issue; how do you get the patient into the study, not out of it.

The other thing that I think we might be able to help with, but I am not sure, has to do with what the response has been on the part of the insurance agencies out there who have tried to avoid the financial burden for covering treatment methods by virtue of referring to this criteria that we establish for purely scientific reasons. It had nothing to do with whether or not it was appropriate to apply the treatment to a clinical situation.

So I would hate to see us getting into that rats nest by virtue of inadvertency in this forum, anyway.

DR. HANLEY: Okay. I think all the issues have been addressed on this. Our job is to provide insight and advice to the FDA. I think we have done that with regard to this.

Question No. 3; imaging studies. Safety; what imaging methods are appropriate for the assessment of material fracture and migration? Effectiveness; which

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radiographic criteria do you believe to be the most meaningful for evaluating device effectiveness? To what degree can radiographic data be expected to correlate with clinical outcome?

We have discussed these issues, particular this effectiveness one. Let's start off with (a), safety; material fracture migration. We have discussed the menu of imaging procedures that we have available.

It has been stated that plane radiography is probably our best tool as long as we can standardize it as best as it can be standardized. Is there a need for other things? Should a protocol include a CT scan, a CQT, an MRI?

DR. TRIPPEL: Some of the synthetic polymers may not show up on plane X-ray. If there is a concern about migration and you need to know where the implant is going, then an imaging method that will reveal its location would, of course, be needed.

DR. BOYAN: One of the things that has concerned me is that many of the materials that are being developed do have a mineral component to them. Without making any statement as to whether that is good or bad, it does have its own inherent radiopacity and we should encourage investigators to consider subtraction radiography to eliminate the contribution of the material to what might not

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be as positive a radiographic result as what it might look like.

DR. HANLEY: I think the simple answer to this question is that the imaging study should be tailored to what we are trying to study. Many times, plane radiography will be sufficient. It is certainly much more cost effective.

But, in certain instances, some of the more sophisticated measuring devices may be necessary.

Effectiveness. Which radiographic criteria do you believe to be the most meaningful for evaluating device effectiveness? To what degree can radiographic data be expected to correlate with clinical outcome? I think we have discussed this also, that the plane film is the best thing we have. There are circumstances where other imaging modalities would be appropriate.

These need to be considered each time. We do not know the correlation between radiographic or imaging studies in the clinical outcome because, in many instances--in all instances, the radiographic features lag behind the clinical situation. In many instances, we have not been able to find a correlation.

So we need to do all. That is why we have suggested that clinical outcome measures from both sides,

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including the patient's side, be performed in addition to other objective measuring studies.

Question No. 4; clinical effectiveness measures. What clinical endpoints and assessment tools are appropriate to evaluate clinical utility? What are the appropriate success criteria for this product keeping in mind that there is an inherent benefit of bone void fillers compared to autograft in that a second surgical site is not required.

Let's start with Question (a). What clinical endpoints and assessment tools are appropriate to evaluate clinical utility?

DR. GREENWALD: I think we have sort of been around this before in a certain light. If we are talking here about patient assessment and clinical outcome, certainly the standardized tools we were referring to yesterday, the Womack, the SF36, are all effective measures of assessing the success of a particular procedure, I would think.

DR. HANLEY: I think so. I will paraphrase what Dr. Nelson had said before which, I think, we have pretty much agreement on. He can comment on this. In order to really do this properly, we need a validated measurement test for quality of life, patient satisfaction, impairment. And it was also suggested that we have, if that is not

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included in those, some type of measurement of systemic health.

DR. NELSON: I think the other issue, as Dr. Clauw brought up, is the issue of the second site and some kind of specialized questions. But I think the issue really is a reliability, validity, that, again, it is related to race, gender, age, those kinds of things that we ask the manufacturer to provide.

If they can't provide it, I think we should ask them to do some pilot studies on the reliability instrument, at least some pilot work to show that it is related and reliable and valid, in terms of patient satisfaction questions and things like that.

DR. HANLEY: Again, I would emphasize that throughout our discussions today and in recent months and years, we want to emphasize how important it is to get the patient's view of how they are doing and separate that from our view which may or may not be biased. It probably is.

DR. RANGASWAMY: But one would still have objective--besides the patient-satisfaction measures, one obviously has objective clinical measures, too.

DR. HANLEY: Right; we would not limit it just to patient-satisfaction measures, but that would be one component of that that is separated out.

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What are the appropriate success criteria keeping in mind that there is an inherent benefit of bone void fillers compared to autograft and that the second surgical site is not required. Dr. Lane alluded to this today that there are seven or ten or 15 or up to 30 percent incidence of complaints and problems associated with autologous bone procurement sites.

Any individuals involved in spine surgery where that is a common thing will know that. So you are out of the--the comparison group immediately is worse off because they have a second surgical procedure. How do you take that into consideration when assessing outcome of these things?

DR. BOYAN: First, I would like to amend it to say that a second surgical site may not be required because there could be instances where it would be--the bone-graft substitute might not completely replace autologous bone graft or marrow.

Certainly, that is why we are doing this. That is the facts.

DR. MAYOR: In addition to that, there are circumstances where autologous bone can be obtained without a second surgical site so both sides of the equation are real.

DR. TRIPPEL: There is yet another permutation on

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that and that is, in some patients, you don't have enough autologous bone left to use so you have to use bottled allograft bone. That would be your control in those instances, in which case, there is no second surgical site.

DR. HANLEY: I would make the case that our measurement tools should measure different things and that the measurement tool will need to measure the radiographic and clinical and patient-satisfaction success of what was trying to be accomplished, be it the healing of a long bone or a spine arthrodesis or what have you.

The measurement tool should also be geared toward measuring the impact of a donor site or lack thereof on the individual patient who is his own control there. I think we have to build that into the system.

I don't think you can deem an acceptable result while these patients--they didn't really heal their fractures but they were happy because they didn't have to have a bone graft versus these guys healed but they didn't have a bone graft.

So we have to sort all that stuff out. I think the tools will enable us to do that as long as we remember that we have to measure each thing that is done or not done to an individual patient.

DR. WITTEN: I do have one additional question

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along the lines of Question 4(b). I would just like to mention the question that actually was posed by the industry speaker during the open public comment session, and that is to ask the panel to comment on the role of bone biopsy in clinical studies given that that would be an additional surgical procedure.

DR. HANLEY: Comments?

DR. BOYAN: I think any time, if a case could be made for bone biopsy, really made for it, I could see a value to it. But in these studies, the information that would be obtained from a bone biopsy could almost certainly be obtained in the preclinical studies.

Then to ask a patient to undergo a bone biopsy on top of the treatment, to me, seems superfluous and actually contraindicated because it is superfluous. But nothing is ever 100 percent. So I could perceive of there being a bone-graft substitute proposed for which a bone biopsy would be absolutely required.

DR. HANLEY: We have discussed that specific issue before. I think we did it yesterday in a different hearing. I would agree. I think you want to minimize the insult to the patient and another surgical insult, if it is not necessary--much of this can be obtained from preclinical testing and can be obtained from--hopefully, almost all of

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it. And then we can monitor clinical progress, success or failure based on the things we have discussed such as the outcome measures and the imaging studies.

DR. FRIEDLAENDER: I would agree with that. I think it gets to a broader issue of burden of proof. There undoubtedly will arise a situation where the burden of proof, by nature of the claim, may require some extraordinary additional assessment.

The other side of that coin is that as we change or expand indications of use from diaphysis to metaphysis and from segmental defects, bone void, arthrodesis, et cetera, that the burden of proof, perhaps, isn't necessarily--it doesn't need to be quite as high.

So I think we need some flexibility both to minimize the extent of burden of proof in expanding indications in some areas and, undoubtedly, with new claims and things that just can't be sorted out, in the unusual case where preclinical and animal investigation is inadequate, I think we have to leave that open as an alternative.

DR. TRIPPEL: I just like to add one more nail to the coffin of bone biopsy. There was a study done by Mascolo a few years ago looking at allografts in which he did biopsy several. He found no correlation between the

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results of the biopsy and the healing of the graft.

As Dr. Friedlaender showed, bone healing is a dynamic process so there may be a biopsy of one area that doesn't show healing yet. In most of the rest of the graft, there is healing.

Secondly, you convert what is a closed situation to an open situation which, in orthopedics, is a very dangerous practice.

DR. HANLEY: I think we have a good consensus on that, that in most instances, we would not think the bone biopsy is necessary, but there may be exceptions.

MS. NASHMAN: At this time, I would like to thank all the panel members and the distinguished speakers for your time, your effort and your energy. I would like to remind the panel members that if you have any of your review material that you would like to be destroyed, you can just leave it on the table by your nameplate.

None of the material provided for today's portion of the panel is confidential so you may feel free to take it home with you. If you have any written notes, I would appreciate it if you would take them home with you. If you leave them on the table, they are fine. If you hand them to me, they become part of the record.

Thank you very much. At this point, I presume the

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meeting is adjourned.

[Whereupon, at 2:15 p.m., the meeting was
adjourned.]