

AT

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ADVISORY COMMITTEE MEETING NO. 48

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Holiday Inn Bethesda
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Tracy Riley, Executive Secretary

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David G. Greenhalgh, M.D.
John L. Hunt, M.D.
Henry Lim, M.D.
Reginald Richard, M.S., P.T.
Robert Sheridan, M.D.
Roger Yurt, M.D.

FDA

Charles Durfor, Ph.D.
Liberio Marzella, M.D.
Michael Weintraub, M.D.
Jonathan Wilkin, M.D.
Celia M. Witten, Ph.D., M.D.

C O N T E N T S**DISCUSSION OF THE CLINICAL TRIAL ISSUES FOR BURN WOUNDS**

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P R O C E E D I N G S

Welcome and Information

1 DR. McGUIRE: Good morning. I would call the
2 meeting to order. I would like to read our charge, which is
3 daunting: "The principal goals of the planned document
4 which we are here to help design is to provide guidance on
5 clinical-trial design issues. Selected pharmacology,
6 toxicology and product-related issues will be addressed
7 primarily with the aim of providing guidance on the type and
8 timing of information that will support a clinical trial
9 and/or references to published guidance documents. The
10 Agency plans to present the first draft of the guidance
11 document at a future advisory panel meeting."

12 Tracy Riley, who is the executive secretary, will
13 read the conflict of interest statement and then we will go
14 around the table and introduce old members and new members.

Conflict of Interest Statement

15 MS. RILEY: Good morning. The following
16 announcement addresses the issue of conflict of interest
17 with regard to this meeting and is made a part of the record
18 to preclude even the appearance of such at this meeting.

19 In accordance with 18 US Code 208, general matters
20 waivers have been granted to all committee participants who
21 have interest in companies or organizations which could be
22
23
24

1 affected by the committee's discussion of clinical trial
2 design for products regulated for the Center for Drug
3 Evaluation and Research, the Center for Devices and
4 Radiological Health, and the Center for Biologics Evaluation
5 and Research intended for the treatment of burn wounds.

6 Copies of the waiver statements may be obtained by
7 submitting a written request to the agency's Freedom of
8 Information Office, Room 12(A)(30) of the Parklawn Building.
9 In the event that the discussions involve any other products
10 or firms not already on the agenda for which an FDA
11 participant has a financial interest, the participants are
12 aware of the need to exclude themselves from such
13 involvement and their exclusion will be noted for the
14 record.

15 With respect to all other participants, we ask, in
16 the interest of fairness, that they address any current or
17 previous financial involvement with any firm whose products
18 they may wish to comment upon.

19 DR. McGUIRE: Thanks, Tracy. Let's do the
20 introductions now.

21 [Introductions]

22 DR. McGUIRE: Thanks very much. The agency is
23 going to give us some words.

24 **FDA Introductory Remarks: Objectives of the Discussion**

1 DR. WITTEN: Good morning. I would like to
2 welcome you on behalf of all presenters at the FDA. As you
3 know, this is the second of two meetings that are going to
4 be held by this advisory panel to address questions related
5 to the design of clinical studies for wound healing
6 products.

7 [Slide]

8 Some of you may have heard some of what I am
9 going to say at the last meeting, but I think it is worth
10 repeating here. There are three FDA centers involved in
11 products for review of wound healing care and I have listed
12 on this slide some examples of the products that are seen in
13 each center. Thus, we have a joint interest in this panel
14 and in helping to move forward on describing the important
15 components of a clinical trial for these type of products.

16 I would like to mention in particular that CDRH,
17 which is my center, regulates wound dressings, including
18 some combination products, biologic or drug components and
19 also all wound dressings. As I am sure all of you know,
20 clinical study design for products for burn wounds presents
21 a challenge for the sponsors and, thus, for FDA in its goal
22 of assisting the sponsors.

23 Some of these challenges that I think are
24 particular to burn wound trials include the fact that some

1 of these products may be an adjunct to other care or are
2 used in conjunction with other care. In addition, the
3 assessment of the effects of the product and surgical
4 technique or judgment critical to its success represents a
5 challenge in clinical trial design. Additionally, endpoint
6 assessment when masking the observer may be difficult and
7 can be a challenge, and this is particularly true in device
8 trials.

9 [Slide]

10 I would like to talk about the role of the FDA
11 wound healing focus group for a minute since this group is
12 responsible for leading us to this point of having a meeting
13 today. I would like to highlight the mission of this group,
14 which is to expedite the development of products for wound
15 healing. It is important to note that the members of the
16 group include reviewers from all three centers and, thus,
17 that is helpful in having this group perform its function,
18 which is primarily to coordinate and communicate between
19 centers on issues related to these products, and with the
20 public, in order to treat similar products similarly.

21 [Slide]

22 The FDA seeks input from and communication with
23 sponsors, professional organizations and other interested
24 parties in developing policy on wound healing. This slide

1 highlights a few of the FDA activities.

2 The first is an FDA-sponsored workshop at NIH, in
3 1993, and the article that is listed here is available
4 outside of this room. The clinical focus group has had
5 several interactions with outside parties, and probably of
6 particular interest for this group is the interaction with
7 the federal issues committee of the ABA.

8 The wound healing focus group is taking the lead
9 on guidance document development for a guidance document to
10 describe important elements to consider in the design of
11 clinical trials for burn products. Asking the panel today
12 for input is an important step in this process. As you
13 know, clinical trial design is not a one-size-fits-all
14 process. Many of the questions we have put before you have
15 complex answers. We seek input from the panel on a range of
16 issues that need to be considered, not just in the care of
17 the patient but in designing a trial to evaluate the effect
18 of a product.

19 I would like to close by thanking all the panel
20 members and consultants who are with us today, as well as
21 all of those in the scientific and medical community and
22 from industry who have come here today to participate in
23 this process. Thank you.

24 DR. MCGUIRE: Thank you. Is there anyone here to

1 speak in the open public hearing?

2 [No response]

3 **Topic 1: Standards of Care**

4 I conclude there is no one. We will go directly
5 to the draft which the members and consultants have. This
6 meeting is staged a little bit differently from our usual
7 advisory committee meeting in that we have a number of far-
8 reaching questions and we have no designated hitters. So,
9 this means that we are here to hear from all of you, both on
10 the advisory committee and the consultants and, please, feel
11 free to participate.

12 As I say, we have a number of things to discuss.
13 Topic 1, and we will take these in the order that the Agency
14 has given to us, is standards of care. The idea here is to
15 somehow deal with inter-center variability in wound
16 management. I will ask each of you to read this paragraph
17 and then we will focus, in a couple of minutes, on the
18 elements of dealing with acute wounds, incision of
19 devitalized tissue, grafting, wound cleansing, dressing and
20 temporary wound coverings, antimicrobials and other
21 therapies.

22 Does everyone have this document that says "draft"
23 on top? Okay, time's up. Put your pencils down and put
24 your hands on your desks!

1 [Laughter]

2 These first questions are quite surgical and I
3 would ask the surgical consultants to address them:
4 tangential excision, excision of devitalized tissue. Would
5 anyone like to answer that?

6 DR. HUNT: Hunt, from Dallas. I guess to get
7 things going from a surgical point of view, for studies that
8 involve burn wounds I think there is certainly terminology
9 that has to be settled. When you say tangential excision,
10 that can be to various depths of a burn wound. So that, in
11 any study, would have to be defined and agreed upon by all
12 participants because you can do tangential excision in a
13 second degree burn and you can do tangential excision all
14 the way down to fat. So, there is perhaps a difference in
15 interpretation of that word because there can be devitalized
16 tissue that is only in the dermis.

17 DR. MCGUIRE: Expand that. Isn't the concept of
18 tangential excision to remove all the devitalized tissue?

19 DR. HUNT: That is correct. Partial thickness or
20 second degree burn has a certain amount of non-viable
21 tissue. You don't have to go all the way through the skin
22 to get to viable tissue. So, it is sort of a misnomer to
23 think that tangential excision means all the way down,
24 removing all the skin, because it does not.

1 DR. MCGUIRE: I used the term because I have used
2 it for years. I didn't mean to imply that it was down to
3 fascia, although in a third degree burn you are down to
4 fascia.

5 DR. HUNT: Well, I didn't mean that. I just
6 wanted to sort of get things rolling, and when you say
7 excision of devitalized tissue, if you don't want inter-
8 center variability that certainly is something that up front
9 has to be clarified very carefully.

10 The other thing is that devitalized tissue, often
11 we do that only with the naked eye and that can vary a great
12 deal even on the same patient with several surgeons. What
13 that gets down to is that you end up perhaps removing living
14 tissue in order to make sure. It is almost an imprecise
15 technique when it is used for deep second degree burns. It
16 is easy to excise all the way through the skin and get to
17 fat but it is imprecise in second degree, which a lot of
18 people will excise and a lot of studies may want to evaluate
19 topical agents on various kinds of burn wounds, and deep
20 second degree burns -- it is accepted under certain
21 circumstances to excise those.

22 DR. MCGUIRE: Would you like to say something
23 about timing of the excision?

24 DR. HUNT: People have said that burn wounds are a

1 cottage industry; every place does something different.
2 Certainly, I think burns exemplifies that, and that is why
3 so many studies are done on donor sites. That is probably
4 the one thing in the burn world, when it comes to topical
5 agents, dressings and various bandages, if you will, that is
6 maybe a little more easily controlled.

7 Timing can vary depending on how many cofactors
8 there are as far as age and size of burn. That is one
9 variable that is difficult to control because all patients
10 are of different ages and have different percent burns.
11 That is one reason it takes so many large numbers of
12 patients in order to get any kind of good statistical
13 background, and that is why perhaps there are so many
14 uncontrolled studies in the burn literature.

15 DR. MCGUIRE: Well, I am sure the Agency hopes
16 that we can bring some order out of this chaos. Yes?
17 Identify yourself for the transcript, please.

18 DR. GOODWIN: Goodwin. Part of the problem is
19 that there are many, many standards of care, and that
20 depends as much on your staffing model as anything else.
21 Now that we have managed care, it is changing even more. To
22 add on to what Dr. Hunt said, if you don't have very many
23 patients in your burn unit and you are not very busy that is
24 one thing. If you have 50 or 60 in your burn center a lot

1 of people wait and allow to heal over longer periods of
2 time. So, I think you probably won't find anybody that does
3 the same thing. I think the system of care in a particular
4 unit that has practiced year after year delivers a very
5 effective and efficient method of care, but it may be
6 totally different from every other burn surgeon here at the
7 table. They probably are equally cost effective and equal
8 in their outcomes but different in what people do.

9 In answer to what John said, some people
10 tangentially excise very shallow to where they get the first
11 bleeding. But there is undeniably dead tissue left behind.

12 DR. MCGUIRE: I have an advantage here, and that
13 is that I am not a surgeon. I don't do this on a daily
14 basis although I have had some experience with burns. I
15 guess some of the major difficulties I have had is
16 predicting what area is actually devitalized because what
17 looks burn to me on day one looks very different on day two
18 or day three. As a surgeon, how do you deal with that?

19 DR. GOODWIN: As I said, it is basically unit
20 specific. First of all, I think probably each of us here
21 that deals with burns has different ideas of when burns may
22 not be excised, and a lot of that depends on non-medical
23 situations, such as staff and how many patients are in the
24 hospital; how much time we have and so forth.

1 DR. SHERIDAN: Rob Sheridan, from Boston. I think
2 there is perhaps a little less variability than all that
3 among the larger centers. I think the standards of care
4 coalesce somewhat, particularly as regards timing of
5 incision. I think that all of us would look at our patient
6 and decide if the wound is a physiologic threat or not, and
7 if that wound is a physiologic threat, i.e., a large burn,
8 we would tend to excise all of the devitalized tissue, less
9 perhaps a few percent, within the first week certainly and
10 achieve biologic closure. I think most of us would strive
11 for that as a standard.

12 DR. GREENHALGH: Greenhalgh, Sacramento. I agree
13 with Rob. To design a study you can't just say take all
14 burns because a burn could be a sun burn, for which you
15 don't do anything, or a burn down to muscle. So, if it is
16 clear that it is superficial and it is going to heal we
17 don't do anything for it, except topical. If it is clearly
18 third degree in a functional area, like a hand or something
19 like that, we can graft that the next day.

20 Then, a lot of the philosophy is that we will wait
21 for some burns that are indeterminate and give it two weeks.
22 We kind of know that if it is not healed in two weeks we
23 will readmit them and then graft them.

24 So, you can't just say take all burns. There can

1 be a great variety of treatments. But really the standard,
2 I would say, for most burn centers is, like Rob said, if it
3 is a major burn, you get rid of the burn wound burden
4 relatively expeditiously. Clearly, third degree burns need
5 to be grafted and for those that are indeterminate you can
6 wait.

7 DR. SHERIDAN: Like Dr. Goodwin says that is the
8 big picture but the details with which those tasks are
9 executed vary greatly from one unit to the next. But,
10 certainly, the principles of getting a big wound off early
11 and an indeterminate wound of small physiologic size or non-
12 threatening size would be allowed to heal, or attempt to
13 heal prior to --

14 DR. GREENHALGH: Well, the healing of a large burn
15 would probably be different than a small burn. I think
16 large burns can have slower healing. So, if you try to
17 compare healing in an 85% burn with that of a 3% burn there
18 are clearly going to be differences.

19 DR. YURT: Yurt, from New York. To answer your
20 question, clearly, it is starting to become apparent I think
21 that there are wound extremes. A full thickness wound we
22 have no problem with; it is the partial thickness that can
23 be either deep or superficial.

24 As you questioned do these wound seem to change,

1 and they do. They evolve over the first 48 hours or so
2 after injury, particularly the ones that are in this
3 indeterminate category, and there still is some difference
4 regarding exactly when those are excised. But I think the
5 big problem tends to be the indeterminate group or the
6 intermediate group. We don't have much trouble with the
7 extremes.

8 DR. MCGUIRE: Do surgeons biopsy to control the
9 extent of necrosis?

10 DR. YURT: No.

11 DR. MCGUIRE: Either pre- or post-excision? Go
12 ahead.

13 DR. MCCAULEY: Robert McCauley, Galveston. The
14 point that I wanted to make is that the real dilemma that we
15 are really seeing here is not so much wounds that need to be
16 operated on but those that are indeterminate. I think
17 unless we can actually come up with some way to have some
18 sort of uniform assessment of indeterminate wounds in terms
19 of whether you believe that they are deep partial thickness
20 and timing of excision there is going to be a lot of
21 variability in any of the studies that come out of this
22 discussion. So, I think that is probably the crux of the
23 problem that we are looking at right now.

24 DR. MCGUIRE: Do you have any suggestions?

1 DR. MCCAULEY: Right now if you look at most
2 wounds subjectively, a lot of burn surgeons would say that
3 probably when we are looking at wounds that may heal in less
4 than 3 weeks we are probably only 50% accurate in making
5 that determination. Certainly with the changing of the
6 wounds that you see within the first week that makes it even
7 more difficult. Also, if you are going to make a decision,
8 it has to be uniform in terms of timing.

9 The only other problem I see is trying to have an
10 objective assessment of an indeterminate wound. I think
11 more recently in the burn literature there have been a
12 number of studies that have come out trying to use more
13 technology and trying to make that determination. Right now
14 I can't quote any large studies that have really been very
15 successful, but I think we are sort of in a stage of infancy
16 in terms of trying to make these objective determinations,
17 and trying to correlate that to our clinical assessment.

18 DR. MCGUIRE: What I am hearing is that the
19 surgeons recognize a great deal of variability in
20 ascertainment of the depth of the wound, and that the
21 management of the wound depends upon the initial
22 approximation of how deep the injury is, and you need
23 techniques to help you with this. Dr. Drake, I think you
24 are next.

1 DR. DRAKE: Just a question. You alluded to what
2 my question was going to be, and that has to do with new
3 technologies. I would like to ask the burn experts around
4 the table, do you rely primarily today on your clinical
5 judgment as to what to do when? Or, are there new advances
6 in technology which are particularly helpful or are
7 perceived to be particularly helpful, such as some of the
8 new imaging techniques? Are there technologies now that you
9 are using, or is it still mainly on a clinical basis?

10 DR. SHERIDAN: Well, my answer would be, along
11 with Dr. Goodwin, that the surgeon's eye is still the best.
12 The trouble is that the relationship between burn depth or
13 thickness and will this wound heal, the answer to that
14 question is not uniform across the body because the skin is
15 of great variability and thickness, and a wound that is
16 thick enough to be a full thickness wound on the dorsum of
17 the hands is superficial second degree on the back. So, the
18 ability of these technologies to determine thickness is of
19 no value across the body. So, there is a very rich
20 literature, going back about thirty years on people trying
21 to make devices to determine the answer to that question,
22 will this burn heal? And, none of them have been uniformly
23 successful.

24 DR. DRAKE: To take it one step further, not just

1 do burns heal but what about debridement?

2 DR. SHERIDAN: Do you mean are you at viable
3 tissue?

4 DR. DRAKE: Yes. Are there imaging techniques or
5 technology to help you?

6 DR. SHERIDAN: They are in development but there
7 is nothing that is as good as the eye of a practiced
8 examiner, in my own opinion.

9 DR. GOODWIN: It is like asking a surgeon to use
10 technology to diagnose appendicitis. You do it by your own
11 physical examination. Burns are the same way. But the
12 bigger problem, in terms of potential trials that you want
13 to design, is totally non-medical. Patients have come in to
14 wait the two weeks that we have heard talked about. Now,
15 because the managed care people say they have to be out of
16 the hospital and it is cheaper to excise and graft these
17 people, they are going to get an operation based on the
18 economics of the issue, not based on your medical
19 indications and the type of decision that you want made,
20 except for big burns, are not going to be all medically
21 driven decisions. These patients are not going to be in the
22 hospital to do these trials.

23 DR. HUNT: One thing that has been introduced over
24 the last five to ten years and has been used recently is a

1 laser Doppler flow probe. It is not as quantitative as we
2 would like, and there have been no good prospective,
3 controlled trials. I think it probably will allow us to
4 tell what is third degree and maybe what is obviously going
5 to heal in a certain period of time. I am sure most people
6 on the panel realize that a burn wound is not like you take
7 an iron and put it on your hand and you have a third degree
8 burn. More times than not it is a mixture. Because of
9 that, the varying depth where one area is deeper than
10 another -- it is just not uniform, and that is why I alluded
11 to the use of donor sites that has been the standard for so
12 much evaluation of burn care products. The Doppler will
13 probably have a place but there may be more sophisticated
14 things. But it is the only quantitative thing now that is,
15 I think, available.

16 DR. GREEN: The issue is not the same thickness.
17 So, if you burn your arm a lot of times the forearm doesn't
18 heal because it has thinner skin. So, there are a lot of
19 variables involved.

20 DR. MCGUIRE: Mrs. Cohen has a question.

21 MS. COHEN: I was just thinking that there aren't
22 MGHS in a lot of places and this is a wonderful opportunity
23 to provide consumers with some information, because the end
24 product is consumers. I think if, in conjunction with this,

1 a brochure could come out -- if a consumer goes to an
2 emergency room, and I imagine that is where they first go,
3 what should they expect and who should be treating them? I
4 think that this would be very beneficial to people,
5 particularly people in small towns. Do a lot of general
6 physicians treat it? Do you need a plastic surgeon? Do you
7 need a general surgeon? So, I think a lot of this should be
8 geared towards what consumers should expect and hope to
9 receive.

10 DR. MCGUIRE: But the standard-of-care depends
11 upon the facility, and in larger facilities there are burn
12 units that deal with it. When you get to smaller
13 communities that don't have a dedicated unit, you are
14 dealing either with general surgeons, plastic surgeons or
15 whoever is expert in that particular area.

16 DR. GREENHALGH: The American Burn Association has
17 identified criteria for transfer to burn units. They
18 realize that a tiny little burn will be treated either by an
19 ER physician, general surgeon or plastic surgeon. They have
20 addressed that question, and they have clear criteria that
21 are published on what burns should be sent to a burn center
22 and what shouldn't.

23 DR. GOODWIN: To amplify on what Dr. Greenhalgh
24 said, the ABA has a web-site and a lot of this initial

1 information is on the web-site. I know that we don't have
2 that yet.

3 MS. COHEN: I can't see someone who gets burned
4 running to a web-site. I mean, that is sophisticated for a
5 lot of people and this country needs to give more
6 information to consumers so they can ask the appropriate
7 questions.

8 DR. HUNT: To answer your question, the majority
9 of burns are small that are really non-problems; they are
10 going to heal. A minority probably needs surgery. Burns
11 are taken care of by emergency room doctors, pediatricians,
12 you name it, I guess even dermatologists, God forbid!

13 [Laughter]

14 It crosses the spectrum of medical disciplines.
15 So many people do take care of burns, and that is because so
16 many burns are just small. But there are areas -- the ones
17 that we really get concerned about are large burns. I think
18 it is important, as was brought up, that there are criteria,
19 and I think that is very important for the consumer to know,
20 and there are centers of excellence that do take care of
21 burns and I think consumers need to be aware of that.

22 Although everyone might not have access to a web-
23 site, the ER physician should be knowledgeable on where to
24 transfer burns and where, in that region, the most care can

1 be gotten.

2 MS. COHEN: Thank you for that response.

3 DR. MCCAULEY: And there is a verification process
4 too for burn centers.

5 DR. BERGFELD: Well, since what we are about today
6 is to help the FDA with guidelines, it seems to me from the
7 conversations that I have heard that any clinical studies
8 would have to involve small wounds, not large, extensive
9 body wounds.

10 DR. GREENHALGH: I would answer that question
11 because I have been involved with some clinical trials, and
12 the problem with small burns or small donor site studies is
13 that there is not much delay in healing and they heal very
14 rapidly, no matter what you do. A lot of small burns, no
15 matter what you do, they will do fine.

16 DR. BERGFELD: Well, maybe we could define small.

17 DR. GREENHALGH: Well, small I would define as
18 less than 3% to 4%. The only studies that have been
19 successful are in Galveston, where they have looked at
20 healing of large burns and using growth hormone, for
21 instance, and that has made a difference. I think
22 clinically it is of no value to put a growth factor on a
23 small wound that is going to heal in three days and that you
24 treat as an outpatient anyway. But where you can make a

1 difference and make it cost effective is if you have a major
2 burn in a hospital and you can shorten their hospital stay,
3 and the studies down in Galveston have shown that that is
4 the way to look at it. For us, doing studies and looking at
5 factors that will improve healing for major burns and
6 shorten hospital stay by a week or two can be in thousands
7 of dollars.

8 DR. MCGUIRE: Let me make this a somewhat
9 artificial stopping place and ask the Agency if you have
10 heard enough about excision, or would you like for us to
11 continue this?

12 DR. WITTEN: I think we could move to the next
13 topic.

14 DR. MCGUIRE: The next topic --

15 DR. MARZELLA: I would like to comment on the
16 issue about studying small burns versus large burns. For
17 the Agency the issue is important so studies would have to
18 have safety and efficacy data.

19 DR. MCGUIRE: Let's go to the next topic which is
20 grafting. We could spend all day talking about grafting.
21 So, let's try to spend part of the day talking about
22 grafting. Dr. Yurt, would you like to say anything about
23 grafting?

24 DR. YURT: Well, there are several different

1 approaches. Most of what we do is split thickness skin
2 grafting.

3 DR. MCGUIRE: Excuse me, I am assuming that the
4 Agency is interested only in -- you are talking about
5 autologous grafts here, or you don't care?

6 DR. DURFOR: I think that we may see several
7 different types of grafting. So, any information that you
8 can give us about grafting would be helpful.

9 DR. MCGUIRE: Go ahead.

10 DR. YURT: So, I will start with autografting.
11 The standard is to try to autograft, that is, close the
12 wound with the patient's own skin. For smaller wounds we
13 tend to use unmeshed split thickness skin graft. For small
14 wounds in areas that are cosmetically important or
15 functionally important we may use a thicker skin graft
16 which, in fact, may require that the donor site be grafted
17 because it is thick.

18 Then for the larger burn injuries where coverage
19 is a problem, we often will take the split thickness skin
20 and mesh it, expand it so that it can cover larger areas.
21 That can go anywhere from about 1.5 times meshing up to
22 about 3. You can go as far as 6 but I don't think most of
23 us go up that far unless we absolutely have to. But the
24 concerns, when using that type of graft, are that both the

1 cosmetic and the functional result will not be as good as
2 using either a sheet graft or a thicker graft.

3 DR. MCGUIRE: My feeling is that the use of split
4 thickness skin graft is fairly uniform among the burn
5 surgeons. That is, there is variability in grafting; there
6 is variability in the depth and most of you are operating at
7 about 0.012 and either mesh or mesh 1.5 to 1.

8 DR. YURT: Yes, and the only other variable I
9 didn't mention is that there is the need many times to go
10 back and reharvest, so that if you reharvest a site you may
11 try to take a thinner piece of skin, and anything that would
12 allow us to take a thin piece so that we could reharvest
13 earlier would also be another thing. But it is much more
14 standard than the discussion you heard earlier.

15 DR. MCGUIRE: Yes, I don't think we need to get
16 into that deeply, but reharvesting a site has a built-in
17 live time. You get re-epithelization quite rapidly and
18 really not wonderful regeneration of dermis. So, you can go
19 back so many times. Maybe there are newer techniques that
20 permit you to go back several times, but there is that
21 healing process, especially if you are dealing with a 60%,
22 70% burn where you have to do major harvesting.

23 DR. YURT: You may want input from some of the
24 other members of the panel but, I mean, typically what we

1 have thought of doing in the past is going back in about two
2 weeks or maybe a little bit longer to recrop, but taking
3 thinner skin. You actually can go back as early as seven to
4 ten days if you are just taking epidermis.

5 DR. MCGUIRE: Further discussion on grafting?

6 MR. RICHARD: Reg Richard, from Dayton. I would
7 like to make just one comment from the rehabilitation
8 standpoint. That is, I think in any study that is done I
9 would like to see reported two pieces of information.
10 Number one is what was the thickness of the skin graft that
11 was taken, and also the location of the body from which it
12 was taken. The reason for that is because burn patients are
13 surviving massive injuries nowadays. The ultimate priority
14 or emphasis is on outcomes.

15 From a rehabilitation standpoint, the development
16 of scar contractures and scar hypertrophy is of utmost
17 importance, and the thickness of the skin graft, because of
18 its contraction and contractibility not only when it is
19 immediately applied when it is harvested, but long-term what
20 its outcome is, is important. I think from a therapy
21 standpoint, to be able to evaluate some of the techniques --
22 I know we will be addressing some of that in the future
23 here, but in order to evaluate some of those techniques,
24 those couple of pieces of information are important.

1 DR. MCGUIRE: While we are talking about it --
2 this is somewhat arbitrary but while we are talking about
3 grafting, do any of you want to discuss skin bank skin, or
4 when you use it and how long you leave it?

5 DR. SHERIDAN: I think probably most of us, if a
6 patient's need for grafting is less than 40%, 50%, would
7 initially approach that by autograft. As those burn sizes
8 escalate temporary covers would be used to close excised
9 wounds because you would excise the wound to prevent the
10 physiologic trap of infection. But then you are left with a
11 wound that needs closure and no autograft to close it, and
12 the standard-of-care has been split thickness cadaver
13 allograft stored in skin banks by pretty uniform standards
14 of cryopreservation, or fresh. That skin can be used either
15 as the sole cover of that wound or, as Dr. Yurt alluded to,
16 if widely meshed skin is used to cover wounds there is a
17 period of time prior to epithelization between those
18 interstices that the wound is basically physiologically
19 still open, and many times an alternative cover like an
20 allograft will be laid over that wound to provide immediate
21 physiologic cover while the autograft is epithelializing
22 beneath.

23 DR. MCGUIRE: Are there other comments on
24 allografts? Yes, Dr. Miller?

1 DR, MILLER: This isn't about autografts but just
2 grafting in general. Are there criteria for grafting versus
3 healing with secondary intention at all? We run into this
4 at our institution where, you know, someone will recommend
5 grafting and the grafting is not done -- not a burn but
6 another type of wound that will heal very quickly with basic
7 wound care. Then the question always comes up would it have
8 healed more quickly if we had grafted. Are there criteria?

9 DR. SHERIDAN: If you had a crystal ball that
10 would tell you this is going to heal in three weeks with
11 topical care, you would, of course, do that because the
12 incidence of hypertrophic scar formation escalates in wounds
13 that take longer than that to heal. I would guess most
14 folks feel that way.

15 DR. MCGUIRE: Other comments?

16 MS. COHEN: One question. You just talked about
17 large wounds, you know, healing much longer than smaller
18 wounds. Are there size criteria where you say this is just
19 not going to do well because it is too large, and you have
20 to do something out of the ordinary, other than letting it
21 heal by itself? I mean, is there a numerical value? Can
22 you put a size on one which you consider so large that it is
23 not going to do well if it is left to its own devices?

24 DR. GREENHALGH: It depends on the area. I mean,

1 if you have a small burn on the face that is third degree,
2 you don't want to let it fill in by itself. It will scar.
3 Or the back of the hand. You know, if you have an entire
4 back that you think is going to heal in three weeks, you
5 know, you can let it go. But if we are worried about the
6 response to injury, a systemic response, usually, say, about
7 25% to 30%, and there is a massive response systemically and
8 you have a metabolic response, yes, then we tend to
9 eliminate the large burn.

10 DR. MCGUIRE: Before we leave graft, I would like
11 to direct a little attention to donor site. Patients are
12 often more concerned about the donor site than they are the
13 recipient site because the donor site is so painful. My
14 impression is that there is enormous variation in the
15 standard-of-care of donor sites from place to place. There
16 are people who still put heat lamps on donor sites to leave
17 the area dry. There are people who are doing just about as
18 far from that as you can get with the permeable or
19 semipermeable dressings. I would like to have the surgeons
20 give us some help on that.

21 DR. YURT: I think you are right. There is a
22 great deal of variability. However, just in the overall
23 picture, I think that if you were going to do a study it
24 would be much easier to get agreement to approach a donor

1 site in a standard way than it might be to get people to
2 change their approach to the burn wound itself, at least to
3 me. I don't get as excited about how I treat the donor site
4 as I might about the burn wound itself, and would be more
5 open to change my approach. But, for example, we use either
6 a Duroderm or Biobrane. If you do a survey, you probably
7 would find, like you said, a number of different things that
8 are used around the country.

9 DR. GREENHALGH: I think you will find that there
10 is no good dressing for donor sites, so that is why they
11 vary so much. I don't think there is any ideal. You would
12 probably find ten different treatments here. But, you know,
13 the philosophy of treatment of a second degree wound with a
14 biologic kind of dressing like Biobrane or keeping a moist
15 environment is important for some. For others, it is to put
16 on something dry. It turns out from most of the donor sites
17 it doesn't make that much difference. You know, maybe it is
18 a difference of a day or two but I think we all treat donor
19 sites differently.

20 DR. MCCAULEY: I think it makes a difference in
21 terms of patient comfort.

22 DR. GREENHALGH: I agree.

23 DR. MCCAULEY: Patients complain about the dry
24 dressings and the exposed ones.

1 DR. GOODWIN: A lot of therapy that you are going
2 to be considering in the future is directed not so much to
3 the two-week healing phase but the long-term phase. It can
4 leave dreadful scarring in some patients. In other
5 patients, who may be lucky, there may not be much in the way
6 of scarring but there will be significant skin mismatches,
7 and patients find this debilitating on a long-term basis.
8 So, I think in terms of healing research in wound care, a
9 lot is going to go into trying to modify that healing
10 response.

11 I agree with Dr. Yurt. I think most people now
12 will use some type of synthetic dressing. Older
13 institutions have used -- the gold standard in the
14 literature is said to be fine-meshed gauze, but I think that
15 is actually a method that decreases the rate of healing, and
16 extends both healing time and patient discomfort.

17 DR. MCGUIRE: Thank you. That is why I brought
18 the point up. Could the Agency tell us if we are going in
19 the right direction?

20 DR. WITTEN: I think this is helpful. In the next
21 topics we would probably be interested whether there are
22 special considerations that relate to full thickness or to
23 partial thickness burns.

24 DR. MCGUIRE: Would the surgeons like to deal with

1 this? What are the selection criteria for split thickness
2 skin graft versus full thickness? You are asking --

3 DR. WITTEN: When we go on to the dressing and
4 temporary wound covering. I know we have talked some about
5 dressings or temporary wound coverings for sites and
6 something about temporary wound coverings in relation to
7 grafting. But when we talk about this topic, some
8 discussion on are there any special considerations for full
9 thickness or partial thickness burns?

10 DR. MCGUIRE: Let's deal with (c) first and see if
11 there is any standardization for wound cleansing. Anyone?

12 MR. RICHARD: I would just start. As Dr.
13 Greenhalgh said, as far as treating donor sites, I think
14 there is great variability in how burn wounds are cleaned
15 from center to center across the country as well. I don't
16 believe there is a standard.

17 DR. SHERIDAN: But I think that everybody would
18 agree on the principles --

19 DR. MCGUIRE: Identify yourself for the
20 transcriptionist.

21 DR. SHERIDAN: Rob Sheridan, from Boston.
22 Everyone would agree that the wound should be kept generally
23 clean and free of debris and accumulated proteinaceous
24 desiccated exudate, and that desiccation should be

1 prevented, and that bacterial overgrowth should be
2 minimized. Basically, all of the varying ways of
3 approaching wounds accomplish those three tasks.

4 DR. MCGUIRE: Are there particular agents that are
5 used to clean the acute wound? Any favorites?

6 MS. CARROUGHER: Gretchen Carrougner, from
7 Seattle. From a nursing perspective, given that oftentimes
8 on the day-to-day care of patients nurses are responsible
9 for cleansing the wound and performing hydrotherapy, maybe
10 in conjunction with physical therapists, I would agree with
11 Reg that there is a great deal of variability in what type
12 of cleansing solution is chosen, and what forms of
13 hydrotherapy is utilized. I think with the development of
14 any clinical trial that is evaluating wound healing,
15 grafting, use of different kinds of dressings, that in the
16 design of the study it should be very clear what type of
17 cleansing solution and to what degree that solution is mixed
18 with water should be specified so that there is very little
19 variability. I think that when one is designing that type
20 of study you could reach agreement between the centers that
21 are participating.

22 DR. MCGUIRE: So, we have identified that as an
23 area of great variability that needs to be standardized.

24 DR. GREENHALGH: I just want to make a comment.

1 You know, I think a lot of us think that it just needs to be
2 kind of washed off with some kind of soap, non-toxic soap
3 and water, and there is nothing really magical about it.
4 You are not going to eliminate bacteria by washing. You
5 basically get rid of the devitalized tissue. So, I don't
6 feel that it is really that big an issue. We use a
7 chlorhexadine type of soap, but it is just kind of washing
8 it off, and then the big thing of preventing desiccation for
9 the partial thickness. There is nothing really magical
10 about it though; it is just to keep it clean.

11 DR. BERGFELD: In the dermatological literature,
12 however, use of some of the antiseptics that you surgeons
13 use are quite toxic to new tissue.

14 DR. GREENHALGH: No, I was saying non-toxic --

15 DR. BERGFELD: Well, non-toxic -- what you
16 mentioned was a toxic drug.

17 DR. HUNT: Hunt, from Dallas. What you say is
18 true, and I think you have to keep in perspective that
19 perhaps in small animal studies that are easily controlled
20 you can find statistical differences of, let's say, 3.5 days
21 versus 4.2 and it may be statistically significant but
22 clinically is not relevant. As far as wound cleansing, even
23 the topical antimicrobial agents won't delay wound healing.
24 It is the slow epithelialization that is sort of a two-edged

1 sword.

2 DR. MCGUIRE: The next issue is dressing and
3 temporary wound coverings. We have touched on that a bit.
4 Frequency and type. Dressing and temporary wound coverings
5 -- we are talking about dressings and temporary wound
6 coverings where we have donor sites to deal with. We have
7 temporary wound covering for the burn site itself, and let's
8 deal with the latter, the burn site itself because we have
9 already talked about donor sites a bit. Temporary wound
10 coverings and dressings for the burn site.

11 DR. YURT: Just to start off, I think, again,
12 there is variability. I would say that most of us probably
13 think that a dressing should be changed twice a day,
14 depending on the type of dressing. Our general approach has
15 been sort of an open dressing, using a topical
16 antimicrobial. We often will put a light dressing on to
17 hold it intact but, in fact, we feel that an open dressing
18 rather than a closed dressing is probably the best approach.
19 But it may be worth getting the opinion of the other
20 surgeons at the table as far as whether they use open or
21 closed, and which topicals they use.

22 DR. MCGUIRE: When you say a light dressing, are
23 you referring to the non-woven fabrics, things like Exudry?

24 DR. YURT: No, something more like Kerlix, just an

1 open-weave gauze dressing to hold it intact but to not limit
2 range of motion.

3 DR. SHERIDAN: Rob Sheridan, from Boston. We
4 would divide the wounds, at least for the purpose of this
5 little topic, into those with overlying devitalized tissues
6 and those without. Those without overlying devitalized
7 tissue would be covered with a temporary wound covering to
8 provide a biological closure and pain control. For those
9 with overlying devitalized tissue, it is dangerous to put a
10 biologic cover on that wound because you get suppuration
11 beneath the membrane, and those patients would be on some
12 kind of open topical while the overlying tissue is either
13 surgically removed or is removed by liquefaction and
14 separation, which I think is consistent with what Dr. Yurt
15 says.

16 DR. MILLER: If the wound is clean and you have
17 debrided adequately, and you have a clean wound and a moist
18 environment, you know, to encourage epithelialization, do
19 you think that frequent changing of the wound can actually
20 disrupt the healing process? You know, once the wound is
21 cleaned the issue of frequency could probably be looked at.

22 DR. SHERIDAN: In those wounds we would probably
23 go towards the temporary biologic cover because then you
24 don't change that at all, and it maintains a favorable

1 environment.

2 DR. YURT: I would agree. I think the only time
3 you wouldn't would be if the wound was delayed in getting
4 that on and there was a concern for possibility of infection
5 on the surface. Then you might still go with a frequent or
6 twice a day dressing change.

7 DR. MCGUIRE: What devices are you referring to
8 with temporary biologic cover? Are you including allografts
9 in that and Biobrane?

10 DR. YURT: There are lots. I am sure all of us
11 use different proprietary brands, ranging from porcine
12 xenograft which works very well, to allograft although it
13 has an expense side to it and I don't think it is what we
14 use for small burns for that purpose. There are synthetic
15 bilaminate dressings you can purchase to that end. There is
16 quite a wide range of choices. They all have the same
17 purpose of providing a vapor barrier and temporary biologic
18 closure.

19 DR. GREENHALGH: I agree with what has been said.
20 You have to be a little careful though. If it is a tiny
21 little burn, just like if you scrape your knee, you don't
22 have to put a \$100 dressing on it. You can treat it with a
23 less expensive ointment and have them change it just because
24 it is a lot more cost effective. You don't have to spend

1 \$100 on some Biobrane to put on a wound. So there is some
2 of that involved also.

3 DR. GOODWIN: I think the main point is that you
4 have to be very careful if you are going to use these
5 membranes, or whatever. You can't put them on top of dead
6 tissue, as many have pointed out.

7 In answer to the other question, if it is a large
8 full thickness burn, for part of the daily assessment of
9 trying to decide whether or not the patient has systemic
10 infection you have to see the burn wound. Many of these
11 wounds continue to slough necrotic tissue for long periods
12 of time. So, I think it is not a process of putting
13 something on a third degree burn and then leaving it on.

14 DR. MCGUIRE: I think, at least in my experience,
15 this has been one of the more difficult problems in
16 predicting just exactly how far the necrosis is going to
17 occur, and what looks pretty good on day one often doesn't
18 look very good on day three.

19 Can the Agency tell me if you have heard enough
20 about grafting?

21 DR. WITTEN: I will just say that this is a
22 helpful discussion. Are there any other different
23 considerations that would apply to partial thickness as
24 opposed to full thickness burns in this discussion of

1 temporary wound coverings?

2 DR. HUNT: Hunt, from Dallas. The very
3 superficial burns, typically scald-induced that you see in
4 pediatric patients, excluding grease, frequently can be
5 handled with a physiologic dressing. The most common that
6 we use, and I am not pushing any certain product, is a
7 heterograft, just meshed pig skin. You leave it on.
8 Probably in the long-run letting that separate in ten days
9 or so may be cheaper than Silvadine. The antimicrobials are
10 not cheap. One can use Biobrane. When you get down to the
11 partial thickness burns, and I don't know if everybody
12 treats them the same way here, but we certainly don't excise
13 anything we can't autograft any more. Burn wound infection
14 is much, much less of a septic threat to patients now than
15 it used to be, even ten years ago. There are people that
16 may do deep tangential excision or superficial tangential
17 and cover it with a biologic dressing. Unit to unit that is
18 different. Then you can use physiologic dressings for third
19 degree burns that you have excised and for some reason you
20 feel you can't autograft. You can use homograft to cover
21 those up. Pig is not a good substitute for that. So there
22 is wide variability depending on the depth, and depending on
23 the individual that is treating the burn, which gets back to
24 the fact that every unit treats it differently. So, when

1 you have a protocol everybody has to sit down and you have
2 to hash through just exactly what criteria to meet. But
3 there are a lot of different uses of different products.

4 DR. MCGUIRE: I am not sure what the emphasis is
5 on for split thickness skin graft versus full thickness
6 because I am not aware that full thickness is used a great
7 deal. So, help me with that.

8 DR. MCCAULEY: I think that usually the standard-
9 of-care for acute patients really is the use of split
10 thickness graft whether you mesh it or use it as a sheet.
11 But I think in terms of reconstruction of patients full
12 thickness grafts play a very important role in terms of
13 final functional and esthetic appearance. So, I think
14 talking about full thickness grafting in an acute burn is
15 probably not going to be very efficacious.

16 DR. GREENHALGH: Except maybe in palms and areas
17 of major function where you don't need very much skin but
18 you need good functional skin.

19 DR. MCCAULEY: That is a good point.

20 DR. MCGUIRE: Antimicrobial agents. Is the Agency
21 interested in topical antimicrobials or systemic
22 antimicrobials?

23 DR. WITTEN: I think we are interested in a
24 discussion of topical antimicrobials. Probably it would be

1 helpful to discuss systemic also.

2 DR. BERGFELD: Can I ask one question also? A lot
3 of literature talks about just emollients, such as Vaseline,
4 put on wounds as being equal to antimicrobials. Would you
5 include that in your discussion?

6 DR. SIMMONS-O'BRIEN: That was one of the things
7 that I was thinking about as well. If one is going to have
8 a study, it would be helpful to know about certain agents
9 that are given an increased risk of antigenicity.
10 Chlorhexadine rinses really came more into vogue or into use
11 because of the horrendous reactions I think we were all
12 seeing with povidone, and many of the surgeons, at least in
13 our field of dermatology, were tending to use Vaseline if
14 the wound is clean, and making their antimicrobial agent
15 maybe the cleanser just to decrease the risk of antigenicity
16 frequently seen with bacitracin and also seen with Neosporin
17 and many of the other antimicrobial agents.

18 I think it has to be factored in, and it is
19 important because, again, a raging contact is going to delay
20 wound healing and might also not be all that recognizable in
21 an individual where there is hardly any normal surrounding
22 tissue as a comparison. So, it might be helpful in a study
23 just to know what the statistical likelihood is of the
24 antigenicity of the preparation that you are planning to

1 use, whether it be the cleanser or the topical preparation.

2 DR. MCGUIRE: Other comments? Yes?

3 DR. GREENHALGH: There are a couple of issues
4 related to that. Number one, if you are dealing with a
5 massive burn antigenicity is a problem because they are
6 massively immunosuppressed. So, that is a difficult thing
7 to study. If you want to do a study with or without a
8 topical, it is fine if it is a tiny little burn; it doesn't
9 matter too much. But if you are worried about the infection
10 issue that is an important issue.

11 As far as my experience with using a lot of
12 bacitracin, if it is put on the healed area it really causes
13 a rash. I think it is probably like a yeast overgrowth type
14 of problem. But the rashes always go away but I am not sure
15 if it is an end to the antigenicity problem or not. But if
16 you are going to get into antigenicity problems, there is
17 massive literature on burns and how the immune system is
18 altered. They don't have delayed hypersensitivity reactions
19 with large burns. So, it is very difficult to look at.

20 DR. MCGUIRE: Other surgeons like to comment?

21 DR. GOODWIN: Actually, I share her opinion to
22 some extent. With some of these topical agents they can get
23 rashes which are due to the topical antimicrobial, and in
24 some patients that will go away even with continued use but

1 in an occasional patient this rash will become confluent and
2 you can get significant superficial skin injury with some of
3 those topical agents. But I think in terms of topical
4 antimicrobials, most of us are talking about ones that are
5 half a square foot or bigger.

6 DR. SHERIDAN: In burns of small physiological
7 size where there is really no risk of systemic infection, I
8 would certainly agree. I think, like Dr. Goodwin says, when
9 the burns get large it really is a physiologic threat to
10 bacterial overgrowth, there must be something in that
11 vehicle, the vehicle being to keep the wound moist to
12 prevent bacterial overgrowth, even if it does mean
13 occasional dermatitis.

14 DR. MCGUIRE: Yes, as Dr. Bergfeld said, in the
15 dermatology business where we are generating injuries but
16 they are clean, the movement has been away from topical
17 antimicrobials. I realize that is not analogous to what we
18 are doing with burns, but we are sort of moving in the other
19 direction.

20 I think what I am hearing is that there is
21 variation from site to site, and there are different
22 indications, but this would have to be controlled in any
23 kind of a study.

24 DR. BERGFELD: Can I ask one other question? For

1 clarification, in the large wounds saline rinses, washes,
2 debridement are used or not used as a cleansing agent?

3 DR. SHERIDAN: That is our routine.

4 DR. BERGFELD: That is your routine. And then the
5 emollient or the topical ointment, as you called it, would
6 then be an antimicrobial in some kind of a vehicle base that
7 added moisture and produced a barrier?

8 DR. SHERIDAN: The goal of the topical agent would
9 be to prevent desiccation, thereby facilitating healing and
10 providing comfort, and to minimize bacterial overgrowth in
11 the exudate that is inevitably coming out of the wound,
12 between dressing changes, and the specific medication or
13 preparation used to achieve those two objectives varies from
14 aqueous soaks and silver nitrate or any other product to a
15 viscous vehicle antimicrobial, like Silvadine or bacitracin.
16 After the wound is cleaned superficially we use commonly a
17 non-antibiotic-viscous ointment just to provide comfort and
18 prevent desiccation, but when wound get larger we use
19 Silvadine or bacitracin.

20 DR. BERGFELD: Well, Silvadine has a zinc oxide
21 base as well. I think that there needs to be more
22 explanation of these topical coverings because I am not sure
23 -- and my husband is a surgeon so I can speak freely about
24 this -- that the surgeons are really aware of what these

1 particular topicals are composed of and what they actually
2 can do for you whether they contain the antimicrobial or
3 not. Sometimes it is the emollient that does all of the
4 work for you.

5 DR. SHERIDAN: That is absolutely true -- the
6 latter part of your comment, I would say --

7 [Laughter]

8 -- our routine on the large wounds is to use
9 silver nitrate, which is an aqueous wet-down to provide
10 those objectives. We actually don't use Silvadine very
11 much, except in outpatients. We use it because it is very
12 easy to use and is painless and easy to apply, and has no
13 metabolic side effects of significance in that population.

14 DR. MCCAULEY: I think most people are aware of
15 the cytotoxic effects of a number of topical antimicrobial
16 agents on both fibroblasts and keratinocytes. I think there
17 has been a push in surgical research to actually try to find
18 solutions which are a little less toxic. In our institution
19 we use quarter strength Dakin's because we can still
20 maintain the same antimicrobial spectrum and, at the same
21 time, preserve the function of the cells that we actually
22 want to heal, to be active to heal wounds. So, I think
23 there is a lot of research in that area but, again, you are
24 going to find a lot of institutional variability in terms of

1 what agents they use on what type of wound, whether you are
2 talking about preoperative wounds or postoperative wounds.

3 DR. MCGUIRE: I can't tell you how that warms my
4 heart. I get criticized for using quarter-strength Dakin's
5 but it is a pretty good preparation. Dr. Rosenberg?

6 DR. ROSENBERG: From a dermatological observation,
7 our badly blistered patients, with toxic epidermal
8 necrolysis and so forth, started not dying when we began
9 sending them to the burn unit surgeons and nurses to take
10 care of instead of us treating them on the dermatology
11 service. So, I think that ought to be clear in the record,
12 that these fellows, at least from our point of view, get
13 better results than we ever got in terms of keeping people
14 from dying.

15 DR. MCGUIRE: Dr. Rosenberg is talking about an
16 extensive disease in which the injury is very superficial
17 and heals rapidly if the patient is taken care of properly,
18 which turns out to be a burn unit.

19 Can we take a shot at systemic antimicrobials? Is
20 there a standard?

21 DR. GREENHALGH: I will just say that studies have
22 shown that we don't treat someone prophylactically with
23 systemic antibiotics and then it basically comes down to if
24 you have an infection you treat them like you do any other

1 patient.

2 DR. YURT: I would agree. I think that we have a
3 very heightened awareness of infection and so we are
4 probably doing more culturing than we would in, say, another
5 trauma patient or something, and most of us I think do
6 monitor the wound in some way to then allow us to select
7 systemic antimicrobials as well as topicals, whether it be
8 biopsy with histology or biopsy with quantitative bacterial
9 count. I think most of us use that, along with standard
10 ways of culturing to guide us in our use of systemic
11 antimicrobials.

12 DR. MCGUIRE: Are surgeons using quantitative
13 microbiology?

14 DR. YURT: That, in fact, in our institution is
15 the only way that we monitor the wound. We haven't been
16 able to convince people to do histology that really can
17 direct us, so we are using quantitative counts.

18 DR. GREENHALGH: We don't, but it is a clinical
19 judgment if you have a wound infection. We don't
20 necessarily go with biopsies and histology.

21 DR. MCGUIRE: It has been in the literature for 25
22 years when Tom Krisik and Robson did it, and I don't know if
23 it is still the standard care. It is hard to get a
24 laboratory to do it.

1 DR. SHERIDAN: You can diagnose the form of
2 infection clinically by quantitative culture, by biopsy, and
3 I think most people think of this as a clinical call looking
4 at the patient, looking at the wound, and supporting your
5 diagnosis. You know, from institution to institution the
6 supportive data will vary from quantitative cultures through
7 histology but it is still largely a clinical call in most
8 places.

9 DR. MCCAULEY: At our own institution we do use
10 quantitative bacteriology a lot. I think it has to do with
11 availability. And we also use the rapid slide technique. If
12 we are in the operating room and you find something
13 unexpected, you can actually do a rapid slide to determine
14 whether or not your counts are greater than 10^5 , and that
15 might affect the type of closure you finally perform. As
16 Krisik had shown back in, I guess, late '60s, early '70s,
17 sometimes it can be very difficult to look at a wound and
18 say it is clean. In fact, in their studies they showed it
19 is about as good as flipping a coin to determine whether or
20 not looking at a wound and saying it is clean versus whether
21 or not it has greater than 10^5 organisms per gram of tissue.
22 And I think it does affect graft take significantly so we
23 use it quite a bit.

24 DR. GREENHALGH: To answer Dr. McCauley, I think

1 in the days when Dr. Krisik did his work, they let the
2 eschar separate spontaneously but nowadays the philosophy is
3 to get rid of the burn wound expeditiously before you have
4 an overgrowth of bacteria, so it means a lot less.

5 DR. MCCAULEY: Yes, and we do that. In fact, we
6 are probably one of the few institutions that still rely on
7 total excision certainly within 48 hours. So we do excise
8 our burn wounds rather quickly but, again, a lot of times
9 you can't cover these wounds totally with autograft so you
10 do rely on allografts, and you may have to have several
11 changes of your allograft before you can proceed to final
12 closure with autografts. So, from the standpoint of
13 bacteriology it is important. I guess since Heggars is also
14 from that institution, it makes it very convenient for us.

15 DR. HUNT: As I think Dr. Bergfeld alluded to much
16 earlier, so many of the studies are on small burns. That is
17 true because there are so many confounding factors that come
18 into play when you have large burns, and systemic antibiotic
19 use is individualized at each unit. As you can see, we vary
20 on what we culture. We don't culture wounds because burn
21 wound sepsis is a non-problem, at least in our institution.
22 Pneumonia is what is killing the patients. But in any study
23 you do have to look at the antibiotics, and the bigger the
24 burn the more likely it is that they are going to be treated

1 for some type of infection. If you are trying to evaluate
2 an anti-infective agent, whether it be topical or systemic,
3 that takes you down to small burns and those are non-
4 problems. I mean, our problem is the big burns; it is not
5 the small ones. So, antibiotic use is extensive in burn
6 units and it will flaw studies when you get to bigger burns.

7 DR. MCGUIRE: Dr. Hunt, just to help me, you are
8 talking about inhalation injury with pneumonia following the
9 inhalation injury?

10 DR. HUNT: Well, you can have inhalation injury,
11 yes, but bronchopneumonia. They may start out with
12 inhalation injury and they may not have it, and it certainly
13 will vary from one institution to another. I am just saying
14 that in our unit bronchopneumonia is a problem. It is not
15 burn wound sepsis that people think of, 10^5 organisms per
16 gram of tissue. With Pseudomonas it looks green on the
17 wound and systemically spreads. That doesn't happen any
18 more.

19 DR. MCCAULEY: In support of that, I mean, in the
20 pediatric population we do a lot more skulls, and a lot of
21 our skull patients die of pneumonia and that is still the
22 number one cause. Pneumonia, I agree, is the key problem.

23 DR. MAYHALL: Mayhall, from Galveston. You may
24 see a little bit of in-house disagreement here. One of the

1 points I would like to make is, you know, when we were able
2 to do full thickness biopsies and we were able to validate
3 our quantitative cultures against the gold standard we knew
4 that we had a high sensitivity and low specificity for
5 quantitative microbiology. Now that we are biopsying
6 tissues somewhere below where the burn used to be, we have
7 no way of validating the quantitative culture. So, really I
8 think it is useful for identifying the agent but we don't
9 have a validated quantitative culture technique, and it is
10 not possible really to make a diagnosis of infection now by
11 biopsy and quantitative culture. You can get the etiology
12 of the burn but we have not really validated that. So, I
13 think it is very important to make that point, that we don't
14 have a validated culture technique at this time for making
15 diagnoses of infection.

16 DR. GOODWIN: Goodwin, San Antonio. I guess I
17 ought to mention what my unit pioneered and considers the
18 standard for diagnosing infection in a burn, and that is an
19 adequate tissue biopsy that contains both the non-viable
20 tissue and the viable tissue. Infection is present if
21 organisms are found in the viable tissue. These may or may
22 not correlate with the quantitative biopsy over a range of
23 two or three logs, but the presence of organisms in viable
24 tissue does correlate fairly closely with clinical course of

1 infection. The Surgical Infection Society has taken the
2 approach that infection means microorganisms in viable
3 tissue where they shouldn't be.

4 DR. MCGUIRE: I think we have finished with the
5 easy things. There is item (f) here, other therapies. What
6 are the other therapies? Does the Agency have anything in
7 mind there?

8 DR. DURFOR: I think we are aware of certain areas
9 that we see routinely and we tried to list those for you.
10 We come to this panel looking to the experts to tell us what
11 else might be out there that are things that we need to
12 consider in terms of confounding factors for clinical
13 trials.

14 DR. BERGFELD: One of the therapies that is done
15 at the Cleveland Clinic on occasion, and we don't have a
16 large burn unit, for skin that is sloughing and people who
17 have diseases where the skin soughs is to do IVs that have
18 component parts including vitamins and minerals. In this
19 case the wounds heal better when you replace zinc and some
20 of the other vitamins and minerals. Is that done anywhere
21 else where you supplement their feedings to enhance healing?

22 DR. GREENHALGH: Yes, that is done at all the burn
23 centers.

24 DR. BERGFELD: But do you add such things as zinc?

1 DR. GREENHALGH: Zinc, vitamin C, glutamine,
2 arginine, all sorts of immune-enhancing agents. We could
3 spend two days discussing whether they are of value or not
4 but they are using that in all the burn centers.

5 DR. HUNT: One short thing, other therapies which
6 every now and then like the phoenix that comes out of the
7 fire is enzymes in treatment of burns. I don't know if the
8 FDA gets approached much any more but periodically they are
9 evaluated in deep partial thickness burns and third degree
10 burns. As of yet, there is no adequate good enzyme that is
11 accepted by I think most people in the burn field. But that
12 would be another therapy that could be used, or that you
13 might be approached as far as second degree burns or third
14 degree burns because, certainly, it is used in decubitus
15 ulcers, and Travase is one. But every now and then somebody
16 has a new product that comes out, but there is very strict
17 regimentation on how you evaluate the burn wound, what kind
18 of burn wound you put it on. It is very important.

19 DR. MCGUIRE: You referred to use of enzymes in
20 decubiti. The use there is quite variable also. Some people
21 use it and it comes into focus and goes out of focus. You
22 had a comment, Dr. Drake?

23 DR. DRAKE: This discussion is very interesting,
24 but most of it is centered around what I would consider

1 thermal burns, and I wanted to know from the Agency if there
2 is any additional information you might need for chemical
3 burns, for example.

4 DR. WITTEN: I am sorry, I didn't hear the end of
5 your question.

6 DR. DRAKE: Most of the discussion is centered
7 around what we would consider thermal burns, burns due to
8 heat, and I wondered if there was any additional discussion
9 or comments that might be needed if one were considering
10 burns due to chemicals.

11 DR. WITTEN: I think we have a whole question on
12 that later in the discussion, where we are asking about
13 that.

14 DR. YURT: Just to follow-up on the question about
15 vitamins and so forth, I think we should emphasize that
16 certainly another therapy is nutrition, and that would
17 definitely have to be controlled. Patients with 30% or
18 greater of the body surface burned will have metabolic rates
19 that really double. So, certainly, a wound is not going to
20 heal unless we give the nutrition. I think that is pretty
21 much a standard but exactly how it is done may vary a little
22 bit from center to center. Enteral feeding is the usual
23 approach.

24 DR. DRAKE: I have another question. What is the

1 status of the current thoughts on oxygenation of wounds or
2 of the total body oxygenation? Over the years there have
3 been scattered reports in the literature and is there any
4 validity to that, or is it used?

5 DR. HUNT: You mean hyperbaric? Is that what you
6 mean?

7 DR. DRAKE: No, not only hyperbaric but there have
8 been some reports in the literature about people directly
9 putting oxygen catheters in and around the wound. There was
10 some stuff presented at the Society for Investigative
11 Dermatology meeting, for example, on some wounds, not
12 necessarily burn wounds but some wounds, chronic wounds.

13 DR. HUNT: Invasive, you mean? They put it in the
14 wound?

15 DR. DRAKE: Yes, they put it in a cover in a
16 wound, sort of like a mini hyperbaric oxygen, but there was
17 also one where they actually inserted a catheter into a
18 wound area. It was not a burn wound; it was a chronic
19 wound. It wasn't decubitus but it was like a leg wound,
20 probably a venous stasis wound. But I just wondered if
21 there is anything in the literature referring to using
22 oxygen in the treatment of burns.

23 DR. GREENHALGH: I think there was a study
24 recently -- I know there was, actually, and they did a

1 prospective study of hyperbaric oxygen and there was no
2 difference in burn wound healing. So, I think most burn
3 centers don't believe in that. I think the topical oxygen
4 is hocus-pocus.

5 DR. SHERIDAN: There have been four studies of
6 hyperbaric oxygen and its effect on the wound per se, and it
7 is not the standard-of-care.

8 DR. MCGUIRE: So the committee comes short of
9 saying that oxygen is toxic.

10 [Laughter]

11 DR. GREENHALGH: You need some but not too much.

12 DR. BERGFELD: I wondered if one might comment on
13 inhalation oxygen, if that enhances the wound healing.
14 Especially if one of your primary death rates is from
15 pneumonia, one might think that they had impaired pulmonary
16 function. The second is that in the decubiti ulcers and
17 even the diabetic ulcers we have seen a resurgence of what
18 they call sterile maggots that are applied to wounds for
19 debriding. Is any of that going on in the burn groups?

20 DR. SHERIDAN: Well, the latter occasionally but
21 not on purpose.

22 [Laughter]

23 In terms of oxygen, I think most of our goal is to
24 keep a physiologic oxygen saturation in the blood at the

1 lowest possible oxygen concentration. I think that is
2 pretty uniform in patients with small burns, 21% room air is
3 what they get to maintain that. In terms of debriding
4 agents, non-surgical debridement via maggots -- I am aware
5 of no systematic use of that in our country although it is
6 used in other places.

7 DR. MCGUIRE: I would like to move to topic 2.

8 DR. MILLER: Excuse me --

9 DR. MCGUIRE: Yes, Dr. Miller?

10 DR. MILLER: I would just like to make one
11 comment. I really do have a concern about the topical
12 antibiotics. You know, someone said we don't use systematic
13 antibiotics to ward off infection, and I think the question
14 still remains, do topical antibiotics ward off infection?
15 Just as there are no real standards among you, folks, there
16 really are no standards among dermatologists either.
17 Tremendous amounts of topical antibiotics are used, and the
18 question is are they efficacious? Do they need to be used?
19 I think the Agency really has to continue to focus on that
20 whole issue. If a study is designed, I think that should be
21 part of it.

22 DR. SHERIDAN: I think it is an excellent question
23 and I agree very strongly that just prevention of
24 desiccation in small wounds is really what you want to do.

1 I think all of us have seen patients with second degree,
2 burns and TENS patients get overwhelming rapid sepsis and
3 die. I think that we are afraid not to prophylax the
4 inevitable overgrowth of bacteria and this proteinaceous
5 exudate in the wounds for that reason, but it may be that in
6 smaller burns that question could be answered.

7 DR. MILLER: And does it work even in the larger
8 ones?

9 DR. MCGUIRE: Dr. Witten?

10 DR. WITTEN: Yes, before we move on I would just
11 like to comment that the panel has had a helpful discussion
12 about many of the factors that inter-center variability make
13 designing a trial a challenge for the sponsors and also for
14 FDA. Before we move on to the next discussion, I would just
15 like to ask the panel if the panel has any suggestions on an
16 approach to clinical trial design that would assist in
17 decreasing this variability in the trial.

18 DR. MCGUIRE: Well, that is really the subject of
19 our day, isn't it?

20 DR. WITTEN: It is the subject of the entire day,
21 and I think just as it relates to standards of care that
22 itself is a challenge, and I think we have heard that
23 different centers do it different ways and it is a little
24 hard to characterize from one center what is done at

1 another. It may be that there is no answer to this. I
2 think this is something we have grappled with at the Agency
3 with the various sponsors, but I just wondered if anybody
4 has any comment on that broad question as it relates to this
5 topic.

6 DR. MCGUIRE: I think one thing that will come out
7 of the deliberation today is that there are a variety of
8 things going on out there, and the first step is to be aware
9 of them so that when you design trials you know which
10 factors to focus on, and there are going to be a lot of
11 them. Topical antibiotics is one out of a lot.

12 DR. WITTEN: That is certainly true.

13 DR. MCGUIRE: So we will just flag them as we go
14 through.

15 DR. YURT: Could I comment on that? Although it
16 does sound like we don't know what we are doing --

17 DR. MCGUIRE: I don't think she said that.

18 DR. YURT: No, there is a great deal of
19 variability but there also is a certain amount of
20 consistency. We haven't talked about a lot of other things,
21 and that is, resuscitating the patient from shock to begin
22 with and getting to the point where we actually are worried
23 about the wound as opposed to the patient surviving
24 immediately. I think, at least in the studies that we have

1 been involved in in the past, there are ways of all centers
2 agreeing that we are going to resuscitate in the first 24
3 hours; that in the second we will use either this topical or
4 maybe a choice of two depending, and standardize it within
5 limits. I think most of us, in the interest of trying to
6 find some of these answers, are certainly willing to modify
7 how we do things. There may always be one center that just
8 absolutely feels they cannot modify to come to some
9 standard.

10 On the other hand, if there is a great deal of
11 variability and it is going to stay that way for a while,
12 then there is really not much point in proving something
13 that is only going to work in one center or in one setting.
14 So I think we have to take variability into consideration as
15 well.

16 DR. MCGUIRE: Good point.

17 **Topic 2: Masking of studies**

18 Let's take a minute and read topic 2. I won't
19 read it to you. It is a large order. I think it is very
20 difficult. It has to do both with the heterogeneity of the
21 patient population and the diversity of therapy, as well as
22 bias, investigator bias. How do some of you deal with these
23 issues?

24 DR. SHERIDAN: I know we have struggled with this

1 one in our unit a lot. What we have tried to do is to sort
2 of have ironclad endpoints that are non-subjective, action
3 type endpoints, you know, the day that a biologic dressing
4 was applied; the day the donor site was reharvested, rather
5 than the day it is 90% healed to a pseudo-biased examiner
6 because really in the actual working environment it is truly
7 difficult to get a truly non-biased, truly blinded opinion.

8 I have often thought about whether it would be
9 useful to hire an outside blinded observer who is certified
10 to make these decisions about is this healed and that sort
11 of thing, and would not be even involved in the function of
12 the unit because typically these blinded examiners are the
13 nurse in the clinic who works for you and knows what is
14 going on, and knows all about the study and is excited about
15 perhaps this working, and it is very difficult to truly have
16 a blind unless you design those kind of action endpoints --
17 total dose of opiate per kilo over the course of the study,
18 that kind of endpoint.

19 DR. MCGUIRE: I think that is exactly what the
20 Agency is looking for. Some of the endpoints in the past
21 have been total healing, and we do need points along the
22 way. Would some of the other investigators like to respond?
23 Yes, Dr. Goodwin?

24 DR. GOODWIN: I would just like to reinforce Dr.

1 Sheridan's comment. I think it is critical actually to have
2 a separate person who, hopefully, is unbiased who is going
3 to make the assessments, and this starts right from the
4 beginning with assessment of the burn injury. If we have
5 four, five residents and a couple of attending and fellows
6 estimating the burn size there can be huge variation just
7 within our own group. In places that have an independent
8 person that comes by and does this at least you get
9 consistency within one therapeutic community. So I think
10 this separate person whose job it is to go around and make
11 these assessments is critical.

12 DR. MCGUIRE: I guess I don't quite see it. There
13 is a peripatetic referee that wanders from center to center?

14 DR. GOODWIN: No, no, I am talking about within a
15 single burn center.

16 DR. MCGUIRE: And that person would not know?

17 DR. GOODWIN: In other words, have someone who is
18 not part of your unit, have a salary line for a nurse from
19 another intensive care unit who is trained and certified,
20 who would sign off on the review sheet saying, "this is what
21 I've found as a blinded observer." I think you are much
22 more likely to get a true blind and a true non-biased
23 opinion than if the investigators -- and I am one -- is left
24 to ask a friend who works for them to be the blinded, non-

1 biased person.

2 DR. MCGUIRE: Sure. Dr. Duvic?

3 DR. DUVIC: I think with video technology
4 available, it raises the option of just taking serial videos
5 of the burns over time and then having a panel of people who
6 didn't do the study judge what happened. I think that has
7 been more and more a reasonable technique to use.

8 DR. GOODWIN: But if I could comment on that, I
9 could make a second degree burn look like a third degree
10 burn, and vice versa, depending on how I manipulate the
11 light in terms of taking the pictures.

12 DR. DUVIC: Well, you would have to have it
13 standardized.

14 DR. GREENHALGH: I agree with Dr. Goodwin. We
15 have kind of toyed with this in the wound healing society
16 for quite a while too and, I mean, pictures don't really --
17 you need a dynamic, kind of interactive evaluation of a
18 wound. Pictures are really hard to evaluate, especially
19 when you get near total re-epithelialization -- you know,
20 the reflection, and is that open or not. I find that to be
21 a lot more difficult. Intuitively, it sounds like it is
22 easy to do but it really isn't that easy.

23 DR. KILPATRICK: I want to reiterate what has been
24 said and ask a question. From my point of view, it is

1 obviously better to have replicated measures, if necessary
2 by different people, rather than subjective evaluations.
3 The question is, in this area of wound healing and burns,
4 are such measures feasible, and what are they?

5 DR. YURT: I think it depends on what in
6 particular you are talking about. For example, if you are
7 studying wound contracture, then obviously it is fairly
8 easy. You can reproducibly take photographs or reproducibly
9 measure and determine in quite an objective way what is
10 going on. The real problem comes when you are starting to
11 talk about texture or even to some extent thickness of the
12 skin and how well it has healed. That becomes much more
13 subjective and I don't know of a good quantitative way of
14 doing that.

15 DR. GREENHALGH: We have published a study looking
16 at surface electrical capacitance. There are ways that you
17 can measure evaporative loss of water and changes when you
18 have re-epithelialized. There are some tools out there that
19 are trying to toy with it. The problem is that there is a
20 bias in the way you place it. You know, that piece is
21 really epithelialized; I will put it there, but if I slide
22 it over towards that open area -- it is real hard because
23 the healing, again, is not totally uniform and it gets to be
24 95% healed versus 100% healed because that one little over

1 there still hasn't healed all the way. Those are some of
2 the other difficulties you have. But we are working on some
3 instruments that may be more objective. They are still not
4 tested. They are still cumbersome and may be more painful,
5 and this kind of thing, but there are some instruments out
6 there we can use.

7 DR. SHERIDAN: I think you really need to think
8 very thoughtfully about what you are trying to achieve. In
9 other words, nobody really cares that much whether it is 95%
10 healed or 90% healed. What they care about is the day they
11 reharvest it, and not the day they say they would reharvest
12 it but the day they actually do because that is what
13 actually makes the difference.

14 DR. GREENHALGH: As long as there are criteria for
15 how you reharvest it, but I think to just as much as
16 possible design that kind of an endpoint. The day a patient
17 is committed to a non-operative course, for example, will
18 vary. That will tell you how well this debriding agent, for
19 example, will allow you to assess burn depth. If you do
20 that on day two instead of day five, that is a meaningful
21 endpoint difference that is going to change the care of the
22 patient.

23 DR. KILPATRICK: There is a problem here. We have
24 heard quite extensively about the variation in standards of

1 care, and I am very sensitive to that. It is obviously
2 implicit in any design that there be an agreed upon
3 protocol, hopefully agreed upon beforehand with the FDA.
4 The question is can the statistician at the FDA expect the
5 surgeons and physicians in a burn unit to follow a protocol
6 when they have the care of the patient to consider?

7 DR. SHERIDAN: I agree with Dr. Yurt that the
8 variability in objectives and philosophy actually is very
9 small. What varies is some of these little details about
10 how you achieve those objectives. I think anything that
11 works has to work in all the environments because the
12 country is not suddenly going to have one list of details to
13 achieve these objectives. So, that has to be taken careful
14 note of and be accounted for that in a study design.

15 DR. YURT: I think most of us are involved in
16 research, and I think that the answer to your question would
17 be, yes, but what it does do, it requires a major up-front
18 prospective commitment to that and understanding that we
19 don't feel like we are going to have to violate those
20 protocols to give good patient care.

21 DR. MCCAULEY: I agree with everything that has
22 been said, but I think one point that we are omitting is
23 that if you are going to look at wound healing in a burn
24 patient and trying to assess different agents, obviously the

1 area that you are going to look at has to be relatively
2 small. Some of the techniques that Dr. Greenhalgh mentioned
3 I think are, again, things that are very early but may be
4 beneficial in the future. Sometimes people have even used
5 digital radio planimetry to look at percent of
6 epithelialization in wounds, and that is very subjective.
7 But I think we have to recognize the fact that even with
8 technology there is still a flaw in assessing the healing of
9 burn wounds because you have to look at variability in the
10 technicians that are performing these studies. Even if you
11 get somebody that is an "expert" to do them, there are a lot
12 of other variabilities in determining the values that come
13 through, patient variabilities.

14 DR. MCGUIRE: Let me put another question out
15 there which relates to one of my clinical problems, not
16 related to burns but related to wound healing. I frequently
17 have difficulty determining when the wound is re-
18 epithelialized. These are children who have chronic erosive
19 problems, genetically driven problems, and they blister and
20 then they attempt to heal, and when I look at the lesion I
21 think that it is re-epithelialized and, in fact, there is a
22 membrane that is a fibrin net with lots of cells in it; it
23 is dry. It is dry and it looks like epithelium. You would
24 think that I would be able to tell epithelium from a chronic

1 non-healing erosion but I don't have good techniques other
2 than biopsy, and I am occasionally caught up short. I
3 biopsy that lesion and find out that what looked like
4 epithelium really is not. Are there staining techniques, or
5 what techniques do you use?

6 DR. SHERIDAN: The same you use.

7 DR. MCGUIRE: Mine is not very good.

8 DR. SHERIDAN: Our problem I think is less acute
9 than yours. In other words, you must be talking about kids
10 with EB, and we see those on occasion, and I agree with you
11 that sometimes it is very difficult to tell if this is
12 exudate or if this is epithelium because it has that same
13 opalescent sort of sheen sometimes. But on donor sites and
14 burn wounds it is not a huge clinical problem, I don't
15 think, for us.

16 DR. BERGFELD: I have a question. I have a sense
17 that the discussion has focused itself on the most severe
18 burns, meaning large areas and perhaps deeper depths, and
19 the study, it seems to me, would have to be sort of an
20 intermediate patient that wasn't that severe but wasn't
21 small, and I guess you have called those the indeterminate
22 group, and then it is modified by size --

23 DR. SHERIDAN: No.

24 DR. BERGFELD: Well, whatever. The second part of

1 this, it doesn't seem to me that you need complete healing
2 as an endpoint. Ultimately, yes, but what you need is that
3 person to be alive and feeling good, and beginning to
4 function. So are there target endpoints somewhere before
5 you get to total healing that one could develop that would
6 be meaningful to say that something was helpful? Obviously,
7 it is time related, I am sure, as to how quickly it happens.

8 DR. SHERIDAN: I think that is a good point. It
9 is, like, day to no dressing change. That is an ironclad
10 endpoint that nobody can kind of bias. I think that is the
11 kind of endpoint you would look for.

12 DR. MCGUIRE: I would like to move on, unless
13 there are specific items that the Agency is interested in
14 that we have missed. Read topic 3 on vehicle controls.

15 **Topic 3: Vehicle Controls**

16 Is there a neutral vehicle? I think you can start
17 with that and work to whether they should be two-armed or
18 how you would design it. For those of you who have designed
19 studies, could you give us some insight to how you deal with
20 the vehicle control?

21 DR. GREENHALGH: I have some opinions. First of
22 all, if you are doing antimicrobial studies, for instance,
23 you want to show that you have a benefit. So, to look at a
24 difference to see if something can reduce infection you get

1 rid of the topicals and see if you go back to the previous
2 standard-of-care. That is one of the issues.

3 The other issue is when you do a wound healing
4 study you have to make sure that your topical as your
5 vehicle doesn't impair healing so that is not a problem.
6 Some of the studies have come out using Silvadine for a
7 topical to look at epithelial healing. I have already said
8 I have a concern about it because Silvadine has been shown
9 to impair epithelialization.

10 So, those are the sort of issues that we need to
11 deal with. So, you don't want to go back to nothing but you
12 also don't want to have an impaired vehicle.

13 DR. YURT: Maybe I can ask you, or whoever made up
14 the question, a question. I guess I have always thought
15 that many of those questions would, hopefully, be answered
16 in pre-human studies, so that I have not been so much
17 worried or I have hoped that the vehicle being a toxin would
18 have already been addressed to some extent. I am sure that
19 you always have to consider that, but is that not often
20 answered prior to this level of study?

21 DR. DURFOR: I think the use of animal studies can
22 be very valuable in this area. I would have some level of
23 question as to whether an animal study can truly predict how
24 a burn patient would respond to a product, and sometimes the

1 applicability of that. So I think the question of the
2 vehicle itself in some respects still remains.

3 DR. SHERIDAN: I thought this was a great
4 question. I have thought about this a lot. Because the
5 vehicle may also be a positive thing, let alone a negative
6 thing as we are talking about, certainly I think it ought to
7 be studied unless it is known that the vehicle is neutral.

8 DR. HUNT: This gets to the point of using the
9 small burn, and for the small burn it is probably not a
10 problem. But I think if there is a vehicle involved you
11 have to test it. And, an easy way to do it when they did
12 enzymes -- I mean, when you did fresh wounds they usually
13 don't become infected. Of course, it was obvious which got
14 the vehicle because nothing happened, at least in that
15 circumstance. One of the things you look for is infection.
16 Certainly, I would emphasize again that to use a vehicle
17 with no antimicrobial control is probably inappropriate
18 unless you can use it on a small burn.

19 DR. SHERIDAN: But you can use vehicle plus
20 standard-of-care. That would be one way.

21 DR. HUNT: Well, standard-of-care would be, let's
22 say, Silvadine and there is vehicle in that. But to take a
23 large burn and have the vehicle and then Silvadine, that is
24 not ethically appropriate.

1 DR. DRAKE: I want to clarify a comment you made.
2 I just misunderstood you. You were talking about vehicle
3 and antimicrobial. Tell me that statement again.

4 DR. HUNT: Well, for the topical agents, many of
5 them will have a vehicle in them. They won't be stand-
6 alone. They will have something else in there that may have
7 an antimicrobial effect, and it may not be that simple. I
8 don't think you can take the risk of putting something that
9 has no antimicrobial, or lesser amount of antimicrobial
10 effect and compare that to the standard. I think that is
11 not appropriate. You have to be sure that you are not
12 jeopardizing the patient and subjecting that individual to
13 increased risk of infection. I think the point that the
14 Agency is making is that the vehicle could be deleterious,
15 but it can also be beneficial and you really have to figure
16 out which way it is tilting the scale.

17 DR. SHERIDAN: Devices also have vehicles. For
18 example, there are membranes with things impregnated within,
19 and that physical vehicle should be studied with and without
20 the add-on.

21 DR. BERGFELD: A question. It sounded like
22 Silvadine is your gold standard for topical, and it is
23 cytotoxic even though there is some enhanced healing in some
24 part of the zinc ointment part. If that is the gold

1 standard, then one would compare the gold standard against
2 any new topical, taking into consideration that the pre-
3 studies coming into the study would have defined both the
4 vehicle for the active drug as well as the vehicle control,
5 and usually that is the same, and you would have some idea
6 of the cytotoxicity nature and also of the healing ability,
7 and also the antimicrobial ability because that can be done
8 very nicely in preclinical studies in animal models, and it
9 can be done in localized wound studies. Before you march
10 into a study that involves a whole body surface you would
11 have to know that. Another part of that is the absorption.
12 If there is anything in the vehicle or the active, the
13 absorption of that through skin, damaged skin, is very
14 important for systemic toxicity. I see that as a
15 preclinical study prior to the actual study.

16 DR. GREENHALGH: First of all, Silvadine doesn't
17 have zinc oxide. It is really a sulfadiazine, silver in a
18 sulfa drug. I agree, people use Silvadine for a lot of
19 their standard care but Silvadine was designed more for the
20 eschar and preventing Pseudomonas invasion and things like
21 that, and it may not be appropriate.

22 What I am talking about when I worry about
23 Silvadine as a control is when studies have been used with a
24 biologic agent versus Silvadine and I think that is an

1 inappropriate control, and you are using something that we
2 know is cytotoxic versus something that is a biologic agent.
3 You all know that if you put a biologic agent over a small
4 wound it is a moist environment, and we all like that; that
5 is important, versus something that has been shown to impair
6 epithelialization. That is why even though it may be the
7 standard-of-care, as Dr. Hunt says, you know, it really
8 doesn't matter what you slap on a wound if it is comfortable
9 and it works okay. People are getting away from that. That
10 is why people have designed things like Biobrane. So if you
11 are going to do, like, a polyurethane dressing which is
12 treated with some kind of agent, you probably should use a
13 polyurethane dressing as a control and not Silvadine. Or,
14 you shouldn't use fine-mesh gauze as a standard because some
15 people have used it in donor sites for years to compare with
16 a biologic agent, because people have shown that dry wound
17 healing impairs healing and, basically, you are slowing the
18 control and you don't know if you are accelerating the
19 treatment arm.

20 DR. BERGFELD: The FDA could respond though.
21 Don't you always compare the gold standard of therapy when
22 appropriate to the new therapy, and it should be at least
23 equal, if not better? Isn't that the route of the decision
24 making?

1 DR. MARZELLA: Care should be taken to maximize
2 the outcome.

3 DR. GREENHALGH: Yes, but the question is if you
4 have a topical agent, biologic dressing that is already on
5 the market versus a biologic agent that has been souped up,
6 you probably shouldn't go back to Silvadine versus the
7 biologic agent that is souped up.

8 DR. MCGUIRE: Silvadine is not getting very high
9 marks this morning.

10 DR. GREENHALGH: Well, Silvadine is important for
11 different reasons. I think for a superficial wound it is
12 not a good choice.

13 DR. MCGUIRE: And that is exactly the point. But
14 I think there still are people using it in areas where you
15 are attempting to re-epithelialize and it is inappropriate
16 to use it there.

17 DR. SHERIDAN: But bacterial overgrowth is more
18 harmful than the cytotoxic effects, and I think that is what
19 David is alluding to.

20 DR. GREENHALGH: Yes, for a large burn that is a
21 different story. So, people tend to mix that up. You know,
22 if you have an 80% burn Silvadine is appropriate; if you
23 have a 3% burn that is superficial, it is probably not.

24 DR. KILPATRICK: As a non-clinician, I would like

1 to make it clear that the FDA is interested in
2 generalizability, and I hear the surgeons drifting between
3 small burns and large burns. I take it from that that the
4 implication is that you cannot extrapolate from small burn
5 trials to the perhaps more relevant large burn issue. Would
6 anybody like to comment on that issue because, obviously,
7 small burns may be easier in terms of a design structure?

8 DR. YURT: I don't think that you can necessarily
9 extrapolate. I do think, in hearing the way the discussion
10 has evolved, that there may be certain aspects of these
11 things that you must first study in a small burn and then
12 carry it to the patient with the large injury. But I think
13 you probably have to do both.

14 DR. SHERIDAN: But, you know, you are rubbing up
15 against some practical issues in that most large burns are
16 in the hospital and most little burns are at home, and it is
17 harder to do a study, like a wound healing study, on an
18 outpatient basis. It is very difficult.

19 DR. MCGUIRE: We are going to visit that issue
20 again later on.

21 DR. KILPATRICK: I have just been told that I am
22 out of order.

23 DR. MCGUIRE: No, I said that was topic 7.

24 DR. GREENHALGH: Well, I will just give you an

1 example. If you look at the EGF, epidermal growth factor
2 trials that were done in the '80s, they showed a statistical
3 difference but they weren't clinically significant
4 differences, and then they repeated it and the wounds heal
5 real rapidly in the small wounds and it is hard to show a
6 difference, and why is it not justified clinically? I mean,
7 you could do a donor site and send them home and it doesn't
8 matter if they heal half a day sooner. So, that is where
9 the big burns where you shorten hospital stay are of more
10 importance to us.

11 DR. LIM: Has there been any study with the larger
12 wounds for any type of epidermal growth factor, cytokine
13 type of issue?

14 DR. GREENHALGH: Yes, the Herndon Galveston
15 studies with growth hormone, and they had to be greater than
16 30% burns, and there were several studies looking at
17 systemic growth hormone versus those children that didn't,
18 and what they showed was that time to first reharvest was
19 about 1.5 days shorter; the time to the second reharvest was
20 2 days, 3 days shorter; and the time to the third reharvest
21 was also shorter. They also showed that they had a
22 significant shortening of length of stay for those patients
23 per percent burn. You know, these are patients with large
24 injuries, but also, you know, it is a cost effective

1 treatment because you have made some economic impact.

2 DR. MCGUIRE: We have gotten a little bit away
3 from the vehicle discussion. I think we are ready to go on
4 to topic 4. Dr. Mindel?

5 DR. MINDEL: Just one comment about the ointment.
6 It seems like what you are saying is that the ointment can
7 be a drug, and the ointment is made up of components. So,
8 you can do a dose-response curve on the components of the
9 ointment. I mean, the component may be water and a
10 hydrogel, maybe two or three different components. But it
11 is possible to handle it as though it is a dose-response
12 problem just like the active ingredient.

13 **Topic 4: Within-Patient Studies**

14 DR. MCGUIRE: Topic 4 addresses within patient
15 studies. I will give you a couple of minutes to read that.
16 One gets the idea from reading topic 4 that there could be a
17 population of patients out there with symmetric and burns of
18 similar depth and size, and I would like for the burn
19 surgeons to address that.

20 DR. SHERIDAN: I think the question is how well
21 the presence of these two sites on the same patient -- will
22 one site influence the other indirectly and how you
23 determine the effect -- you know, where is the systemic
24 effect coming from? I wonder if perhaps you randomized

1 every fifth patient to standard-of-care alone but studied
2 them the same way if that would sort of pull that data out
3 of the population.

4 DR. MCGUIRE: I am missing it. You think that you
5 do not have a population with symmetric --

6 DR. SHERIDAN: The question is if you have one
7 patient with two treatment sites, how will you determine the
8 etiology of the systemic effect? That is how I read this.
9 In other words, if there is a systemic problem, how do you
10 know if this is secondary to the study site or the control
11 site, or the study material or the control material? And,
12 the only way to do that really is to have a standard-of-care
13 alone randomized patient to study.

14 DR. GOODWIN: My interpretation is that you are
15 looking at comparing the effect on healing of two different
16 types of agents. That is where the sort of fairly
17 standardized donor site model comes from. Although the
18 paragraph doesn't mention it -- you do when you say
19 symmetric, but if you are going to use this type of model
20 they almost have to be mirror images of each other on the
21 body. You can't compare a piece of plastic on the back
22 versus a piece of plastic on the forearm.

23 DR. MCGUIRE: Dr. Witten, give me some sense of
24 the question.

1 DR. WITTEN: Well, I think the question was as
2 described. If you are studying a product and the control on
3 the same patient, but you see in the trial some systemic
4 toxicity that might be unexpected, something that could
5 increase infection or some other systemic toxicity, like
6 sepsis, how would you determine whether that is related to
7 the product or to the control? I think the one suggestion
8 that was made would certainly be one of the ways to address
9 that, that is, to incorporate some patients with only
10 control therapy into the study design.

11 DR. GREENHALGH: I think you need to go back to
12 the phase I, II, III kind of model. You do the toxicity
13 studies and then go back and do the later studies, and if it
14 is one versus the other, you know, what is the specific
15 question? You heal better or you don't heal better. Yes, I
16 guess you can go back and look at the differences in
17 toxicity but I think those are separate issues.

18 I still think that having a patient as their own
19 control is the best way to do it because it is hard to
20 compare an 80-year old diabetic person with a decubitus to a
21 20-year old paraplegic who is otherwise perfectly healthy.
22 There is a lot of variation between the different patients,
23 and you can get a burn patient with bilateral hand burns,
24 for instance, or bilateral leg burns and compare the two.

1 But if the question is where is the toxicity, that
2 is a different question I think, so it depends on what your
3 question is. If you are looking for toxicity, then that is
4 a whole different type of study.

5 DR. MCCAULEY: I think what we are hearing really
6 is not so much systemic toxicity, but what you are really
7 going to try to get at is local infection and delayed wound
8 healing. Isn't that right?

9 DR. DURFOR: That would be available within-
10 patient studies I guess, but then there is the question of
11 is there a control of systemic effects.

12 DR. SHERIDAN: And also the interactions,
13 especially if we are incorporating all this variability in
14 study design between centers. I mean, there are unknown
15 interactions between study agent and therapy Y, which is on
16 the third part of the body, which is the rest of the
17 patient. The only way to account for that is to randomize a
18 certain percentage of the patients to standard-of-care.

19 DR. GREENHALGH: Well, if you have a toxic
20 treatment, yes, you need to worry about that. Most of these
21 are fairly innocuous as far as that you can do the
22 preliminary phase I and show that most dressings we use
23 don't cause a lot of problems with systemic toxicity. They
24 can, I suppose, but they are relatively safe. They are

1 tested. So, we have a very low rate of systemic toxicity.
2 So, if the question is are they efficacious or are they
3 toxic, I think you have to ferret out those two questions.

4 MR. RICHARD: I think another point that might
5 already have been mentioned though is the importance of
6 using mirrored sites on the body. An example would be if we
7 are going to be looking at donor site dressings, I would
8 guess that a donor site on the back would heal much
9 differently than a donor site on a thigh or on the leg, for
10 example. So, mirrored sites is an important factor in
11 looking to compare one substance or one item to another.

12 DR. MCGUIRE: And a 0.2 mm thick harvest will heal
13 differently from a 0.3 mm. It is really amazing. Other
14 comments?

15 DR. GOODWIN: If you are talking about using a
16 patient as his or her own longitudinal control, you probably
17 can't do that, at least in patients with reasonable size
18 burns. A patient on post-burn day four is a different
19 patient on post-burn day ten. So, if you had sort of a
20 crossover design, you probably couldn't do that.

21 DR. KILPATRICK: This is, indeed, a design of
22 experiment question and, as has been brought out, I think
23 there are two basic ways to go. One is the serial approach
24 where you go through a phase I, phase II, phase III approach

1 and establish what is important in terms of systemic
2 reactions. I think the question begs for a complex design,
3 and there are such, indeed, where you might have multiple
4 objectives from the clinical trial.

5 I hesitate to recommend such a design. It might
6 be all right in agriculture but it is certainly not feasible
7 in burn patients -- and this is quite serious -- because of
8 the limitations of patient care.

9 DR. MCGUIRE: Other comments? Yes?

10 DR. DURFOR: I appreciate your comments, Dr.
11 Greenhalgh, about phase I, phase II, phase III design.
12 Given that these patients are predisposed to a lot of other
13 intercurrent events. Could you give us any guidance on the
14 design of a phase I, phase II studies that would allow you
15 to, either in a controlled or uncontrolled manner,
16 understand the toxicity associated with the problem?

17 DR. GREENHALGH: Well, you could do a double-
18 randomized trial if you are looking at toxicity. It depends
19 on what you are using whether you can blind it. Those
20 studies are done also, you know, where one patient gets it
21 and one patient doesn't. It is done in a blinded fashion;
22 it is randomized. Then you can look for what kind of
23 toxicities you might have.

24 The concern with burn patients is that survival is

1 so good now that it is harder to show a difference in
2 mortality unless you really get large numbers. Most of our
3 patients have small burns and the number that have very
4 massive burns is a lot smaller. So, mortality studies are
5 very difficult to do because we just do better with our
6 survival statistics. You know, infection rates are low. We
7 don't have those as big problems. So, if you are looking
8 for those kind of toxicities I guess you would need multi-
9 center trials.

10 DR. DURFOR: Thank you.

11 DR. MCGUIRE: Other comments?

12 [No response]

13 **Topic 5: Assessment of Burn Wounds**

14 Let's aim for a break at eleven o'clock and deal
15 with topic 5 before we take a break. Topic 5 is the
16 assessment of burn wounds. Standard methods for wound
17 assessment are critical to clinical trial design when
18 defining study populations, monitoring patient safety, and
19 evaluating product efficacy.

20 Please describe techniques that might be used to
21 assess the depth of partial and full thickness burns,
22 subjective clinical assessments and quantitative methods.

23 We discussed that a little bit early on. Dr.
24 Duvic?

1 DR. DUVIC: I think one thing that hasn't been
2 mentioned is the 20 mHz ultrasound technique that can assess
3 epidermal thickness, and then what is going on in the
4 dermis. We have used it to assess the depth of skin
5 lesions. I don't know whether it has been applied to burns,
6 but perhaps that might be a useful technique to try.

7 DR. MCCAULEY: I think it has. I think some
8 institutions have actually used the 7.5-10 mHz ultrasound
9 and have been able to quantitate depth of injury up to about
10 0.1 cm, I believe. But, again, these are not large studies.

11 DR. SHERIDAN: And also, as David Greenhalgh
12 alluded to, there is the sampling error inherent in any kind
13 of device that looks at a piece of a wound. There is
14 nothing out there that will reliably do that. So, you need
15 either an honest blinded assessment by an experienced
16 examiner or you need an action endpoint like was the wound
17 grafted, yes/no? And, that will tell you whether this was a
18 deep dermal or full thickness injury or not.

19 DR. GREENHALGH: Don't forget that wounds evolve
20 too and if you are not perfusing very well, a second degree
21 burn may end up getting deeper and not heal. So, they
22 change with time also.

23 MS. CARROUGHER: I think the point that some
24 people have made is that people rely primarily on clinical

1 judgment when the patient is first admitted, and then
2 revisit that the next day and possibly the next day after,
3 and continue to reassess, and that is pretty much the
4 standard-of-care. Aside from maybe certain identified
5 technology, but it pretty much is clinical assessment.

6 DR. MCGUIRE: It was clear from the response to
7 the question I posed earlier that you don't do multiple
8 biopsies to determine depth of injury. I guess biopsy seems
9 such an easy thing to do for a dermatologist that that leaps
10 to mind, but it is not part of the practice of assessing
11 damage.

12 DR. YURT: Again, I think part of the problem is
13 if you are dealing with a relatively large wound and there
14 is variation in the depth of the skin, as well as the depth
15 of the injury or the length of contact that occurred in
16 certain areas. So, we can't rely on a biopsy low on the
17 forearm to tell us what is going on up near the elbow.

18 DR. MCGUIRE: Oh, we do lots of biopsies.

19 DR. GREENHALGH: But there is also the morbidity.
20 We wouldn't have a patient left; we would chew him up with
21 biopsies.

22 DR. SHERIDAN: And also these are all open,
23 contaminated wounds through which you would be doing
24 multiple biopsies and introducing an element of morbidity

1 that may not be acceptable.

2 DR. GREENHALGH: We have talked about biopsies in
3 my former institution, and our mentor was dead against them.
4 We were trying to prevent scarring and so making multiple
5 holes in our patients is hard to do, and they leave scars
6 and we don't want to do that to our patient. So, just doing
7 biopsies on a patient, there is some resistance to doing it
8 not only by the patient but by the physician.

9 DR. BERGFELD: I would like to comment on the
10 biopsies, being a dermatopathologist. There are
11 variabilities, and the variability of the pathologist to
12 interpret what you give them with all the variables coming
13 into it, then the variables in the interpretation are just
14 as wide. I don't think it offers you much more than your
15 clinical experience. I also say that about the tissue
16 biopsies for culture. The same thing prevails in that
17 arena. So, I am not sure that that adds anything but more
18 confusion.

19 MR. RICHARD: I think another way to address what
20 Dr. Sheridan was saying about making sure you are looking at
21 the same site all the time is to simply use a template to
22 put over the wound, and every time you go back to assess
23 that wound you have an area demarcated on a plastic film,
24 much like you trace the pressure ulcers and go back to that

1 same site every time to ensure that we are looking at the
2 same area.

3 DR. DRAKE: I am not sure that death is so much
4 the issue as the viability because you have explained very
5 clearly that on the hand the depth is a really different
6 factor than a burn on the buttocks, for example. The depth
7 doesn't seem to be the issue; the issue seems to be
8 viability.

9 DR. SHERIDAN: Burn thickness is of no value.

10 DR. DRAKE: So this is not an important variable
11 to measure, but measuring viability of a burn injury would
12 be. Is that correct?

13 DR. GREENHALGH: Depth in relationship to the
14 thickness of the skin. You need to remember the thickness
15 of the skin.

16 DR. DRAKE: But is it still the depth issue or is
17 it how viable the injury? How viable is that burn injury?
18 In other words, does it have a good blood supply? I am not
19 a burn surgeon but I did three months on burn surgery and
20 what that served for me was to give me a healthy respect for
21 the burn surgeons because that is the hardest work I ever
22 did, and it is very complex. I loved it but it was very
23 hard. It seemed to me that taking it down to where you have
24 pin-point bleeding is still a measure. It was then; it

1 seems to still be a measure today when you are looking at
2 debriding and you are trying to determine how viable the
3 tissue is, just as much as clinical inspection for infection
4 is. It seems to me that the depth is not the issue; it is
5 the viability of the wound.

6 DR. GREENHALGH: You are right, and it is not only
7 that but also if it is a hand burn and it is healed in two
8 weeks, it will probably be okay. If it is healed in 3.5
9 weeks, you will perhaps have significant scars and
10 functional problems. And, there are so many variables that
11 it is hard to predict. For example, an 80-year old skin is
12 much thinner than a 20-year old's. There is a variability
13 there in how well perfused they are. So, there are so many
14 variabilities. That is why if we are not sure, we may wait.
15 Send them out as an outpatient and they would have to come
16 back. There are a lot of variables involved.

17 DR. DRAKE: I have a follow-up question. If you
18 are assessing, instead of just looking at the depth might a
19 ratio be helpful? I mean, you just alluded to that, a ratio
20 of the depth of the wound with respect to the skin in the
21 area that you are working in. In other words, if you
22 developed an assessment that involved a ratio, would that be
23 more helpful or more useful in terms of interpreting data or
24 collecting data?

1 DR. GREENHALGH: If you can get those numbers
2 reliably, and there are not really good ways to do it
3 because you also get a layer of dead tissue over the surface
4 sometimes that is non-viable skin. You know, how much of
5 that is there? There are edema changes. There are a lot of
6 variables.

7 DR. YURT: I think that what you are saying is
8 true. As we indicated before, we can do pretty well
9 clinically with a full thickness burn versus a partial
10 thickness burn. But the real question would be not only how
11 deep the partial thickness burn is but how much epidermis is
12 left because that directly relates to the rapidity of
13 healing, as well as the cosmetic and functional results.

14 DR. SHERIDAN: And I don't think our clinical
15 calls are as bad as has been said. I mean, it is uncommon
16 for me to feel that I have really made an error in calling a
17 burn. It happens but it is not a routine kind of thing.

18 DR. MCGUIRE: I guess clinically I have had
19 difficulty in determining what the extent of the burn is
20 because there would be a clearly defined injury here, and
21 then when I examine the patient 24 hours, 48 hours later
22 that was only part of a larger field that clinically looked
23 pretty good to me initially and I find I have made a
24 mistake.

1 DR. HUNT: I think when it comes to wound
2 biopsies, if you are trying to assess healing on a
3 microscopic basis, you are probably not looking for clinical
4 significant changes, and I want to see something that I can
5 tell grossly. I am not really interested if something is
6 going to take maybe one day longer, or histologically this
7 area healed and maybe the one next to it didn't. I want
8 something that is going to show me grossly a big difference,
9 and you are down on the microscopic level.

10 It is interesting that burn surgeons deal with
11 open wounds, yet we seem to be very reticent to biopsy
12 wounds. I think a lot of that is because the studies are
13 often on donor sites and it comes up, "let's biopsy a donor
14 site" and, just like Dr. Greenhalgh said, we don't want to
15 biopsy them. They scar. We probably are just overplaying
16 that a little bit.

17 But biopsies I certainly think will be important
18 in some of the future burn research. I think biopsies may
19 very well be very, very important in assessing scar
20 maturation and various agents that might affect that. I
21 think there, from a molecular point of view, biopsies will
22 be very important to consider for a study and I think most
23 burn surgeons probably will be very agreeable to do that.
24 But when you are talking about how deep this is, and does

1 this second degree heal, and you want to assess it by
2 microscopic assessment -- I guess, to me, I want to see
3 something; I don't want to see it on a microscope.

4 DR. MCGUIRE: We all want to see something. I
5 think the Agency wants to know how we can predict or how we
6 can stratify these patients.

7 DR. GREENHALGH: I just want to tell you the
8 advice of my wise old mentor from Seattle, Dr. Heinbach. If
9 you have a small burn on the back of your hand and you are
10 not sure, he says don't make the decision. Just send them
11 home, have them do therapy and put them on a topical, and
12 come back in two weeks. If it is healed, fine; if not, we
13 will graft them. So, a lot of times we will defer the
14 judgment. We don't have to predict the future if they can
15 deal with it as an outpatient. So, we will avoid that
16 decision a lot of times.

17 DR. MCGUIRE: That is good for clinical care, but
18 I am not sure it helps you design a study. But that is
19 excellent clinical care.

20 MR. RICHARD: Dr. McGuire, I think you brought up
21 a good point about that burn wound, and if we are talking
22 about clinical trials one thing that an institution doing a
23 clinical trial, particularly multiple site trials, needs to
24 decide is what post-burn date therapy is to begin, because

1 burn wounds are dynamic and, as you said, they do change,
2 and it should be standardized as to what point in time the
3 therapy actually began, not only the endpoint.

4 DR. BERGFELD: Or when the assessment is
5 finalized.

6 MR. RICHARD: Right.

7 DR. BERGFELD: The major assessment.

8 DR. SHERIDAN: That is what I was going to say, to
9 account for that in your study design. When the patient
10 comes in with three burns, if it is a superficial burn it is
11 going to heal, you are sure. If it is a full thickness burn
12 it is not going to heal, you are sure. If it is
13 indeterminate -- and those indeterminate burns then go on to
14 a track of evaluation that typically, in our unit, on day
15 five we say this is going to be a non-operative track or an
16 operative track. You just incorporate that decision process
17 on those three burns at presentation into your design. Many
18 of your agents are designed to help facilitate to shorten
19 that period to the final determination. For example, one of
20 the proposed uses for debriding agents would be to shorten
21 the period of basically spontaneous separation, which is
22 what you are waiting for to happen at day five to allow you
23 to make that judgment.

24 DR. YURT: I was just asked to maybe enunciate

1 what the clinical criteria are that we use, at least in the
2 extremes. I mean, a full thickness wound is leathery, dry,
3 has thrombosed blood vessels, is insensate, and is to all of
4 us clearly a full thickness wound.

5 The ones that are bright red, moist, sensate, and
6 painful are the ones that are partial thickness and are the
7 ones that we have somewhat more difficulty in determining
8 until maybe four or five days.

9 The other thing, just to follow-up on your comment
10 about looking at the wound at one time and seeing it
11 different the other just emphasizes the fact that these
12 wounds do evolve and, certainly, if we get an 80-year old
13 with 30% burn, you can look at it when they first come in
14 and it looks like it might qualify as partial thickness, and
15 if they have a difficult resuscitation over the next 24
16 hours it will be full thickness in 24 hours. So, you have
17 to look at the time that you are evaluating the wound as
18 well.

19 DR. MCGUIRE: We are about to take a break. Does
20 anyone have any pressing item on this? If not, let's
21 reconvene at 11:20 and we will start with topic 5, question
22 number 2.

23 [Brief recess]

24 DR. MCGUIRE: If you will return to your draft,

1 you will recall that we were discussing topic 5, assessment
2 of burn wounds, and we have finished discussion on the first
3 item under topic 5, and we are now ready to discuss part 2
4 under topic 5.

5 Please indicate how wound infection might be
6 evaluated and monitored, e.g., clinical, microbiological,
7 and histological assessments as well as monitoring systemic
8 effects, wound healing and graft take.

9 Let's stop that sentence at "microbiological and
10 histological assessments" and then we will deal with the
11 other part of it in just a minute. We have actually
12 discussed clinical, microbiological and histological
13 assessments to some extent but let's discuss them further.
14 Yes, Dr. Sheridan?

15 DR. SHERIDAN: There is a recently developed
16 clinical set of burn wound definitions, developed by a
17 subcommittee of the ABA, that might be of utility here. It
18 was designed specifically to address this issue of inter-
19 center variability and definitions of infection to allow
20 communication and facilitate multi-center trials. It so
21 happens that the first author of that is sitting in the
22 audience, but that might be of utility, and I am sure we
23 could get a copy of Dr. Peck's definitions for the
24 committee.

1 DR. MCGUIRE: Thank you. Further discussion on
2 that?

3 DR. BERGFELD: I would like to ask a question
4 about clinical assessment. That is, one is on infection and
5 one is on possible contact dermatitis. Obviously, it would
6 depend on the initial and then the following examinations.
7 Contact dermatitis might be in the following as well as the
8 infectious. But is there anything in the standard of
9 grading these that incorporates irritant or allergic
10 dermatitis due to a topically applied agent?

11 DR. MCGUIRE: No.

12 DR. BERGFELD: I would say that that is needed. I
13 wonder if the Agency could direct us here. We discussed
14 infection and quantitative microbiology earlier. Is there
15 more information that you need from us?

16 DR. DURFOR: Wound infection is a very important
17 aspect in clinical trials in endpoint and in adverse
18 assessment. There are many different ways of measuring
19 that. So, what we are looking for, in terms of how patients
20 are treated, is what is the most predictive indication of an
21 infection that then becomes important, and how can people do
22 either an endpoint or an adverse assessment in the most
23 objective manner.

24 DR. MCGUIRE: Would someone like to address that?

1 DR. MAYHALL: I looked at those new definitions
2 proposed by the ABA. I saw them several months ago. One of
3 the problems, of course, in doing studies is that they
4 pretty much acknowledge that most of the centers, I guess,
5 have done early excision and they are not going to be doing
6 full thickness biopsies of eschars and, therefore, all the
7 definitions are pretty clinical. So, there is going to be a
8 lot of subjective assessment of burn wounds and,
9 unfortunately, it doesn't seem that we are going to have
10 anything that has provided more objective type of diagnostic
11 tools for clinical trials.

12 Again, at this point I would like to say that I
13 agree with Dr. Goodwin that the gold standard is seeing
14 organisms invading viable tissue below the burn wound and a
15 full thickness biopsy, but now that we don't have much to
16 biopsy in the way of burn eschar, the biopsies that are done
17 have not ever been validated, and people are doing
18 quantitative cultures but there is no gold standard against
19 which these quantitative cultures have been validated. So,
20 unfortunately, I think we are kind of left at this point --
21 I think that cultured biopsy material is useful for
22 establishing the etiology once you have diagnosed burn wound
23 infection, but I don't think we currently have an objective
24 way of making the diagnosis. So, I think that is going to

1 be a problem for clinical trials.

2 DR. GOODWIN: Just to add some defense to that, I
3 guess we are a little slow so we still have a little bit of
4 eschar to biopsy at times, but I think the general principle
5 of finding organisms invading into viable tissue probably is
6 an inaccurate reflection of the presence or absence of
7 infection. We get other types of disease, and even the TENS
8 wound will get infected and the biopsies appear to be quite
9 accurate in predicting infection if there are organisms
10 invading the viable tissue.

11 DR. GREENHALGH: I think as far as assessing
12 infection, you have to be careful not to take a swab because
13 you will have bacteria around wounds all the time. But did
14 the infection alter the care? For instance, if you are
15 looking at a graft, did you lose graft because of purulence
16 in the wound, or is the graft take substandard? That is an
17 indicator you can look at. Does a partial thickness burn
18 become full thickness because of invasion? So, I think it
19 is some functional change -- you have to regraft; you have
20 lost more graft than you should have; you have to change
21 your therapy. It is more important than whether you got
22 Pseudomonas on that swab or not.

23 DR. MCGUIRE: I may have made a mistake here. I
24 thought when we were talking about quantitative microbiology

1 that you were talking about numbers of organisms in a tissue
2 sample.

3 DR. GREENHALGH: In a viable tissue sample.

4 DR. MCGUIRE: Okay. Dr. Orkin?

5 DR. ORKIN: How often does one see a saprophytic
6 organism that we would ordinarily consider saprophytic
7 invading and playing a significant role?

8 DR. GREENHALGH: It depends on what you call
9 saprophytic.

10 DR. ORKIN: Candida, or any organism that would be
11 standard on the skin but not the usual Staph. aureus
12 coagulase positive, from the skin point of view, playing a
13 role because of the open accessibility and the immunologic
14 deficit of the individual.

15 DR. GREENHALGH: I think it is regional. In Texas
16 there are a lot Aspergillus spores or whatever in the air.
17 So, we occasionally will get invasive Aspergillus infection
18 in burn patients.

19 DR. HUNT: It is unit specific. We never see
20 Aspergillus. Thank goodness, it stays down there.

21 [Laughter]

22 Our common pathogen is MRSA. So it depends on the
23 burn unit where you are. You know, 15 years ago it was
24 Pseudomonas pretty much uniformly around the country in burn

1 units. We don't have that any more, do we?

2 DR. GREENHALGH: Not much.

3 DR. HUNT: No.

4 DR. SHERIDAN: But I think incorporating what
5 David said about the need to just have some action being the
6 endpoint, you know, that eliminates a lot of variability in
7 definition sets. It is just not going to be possible to
8 have a very exact yes/no kind of endpoint unless it is an
9 action-based endpoint. Is the patient treated for burn
10 wound infection? You know, that would be the endpoint.

11 DR. MCGUIRE: That would be a very crisp endpoint
12 that would translate from one center to the next center.

13 DR. BERGFELD: Excuse me, would it be systemic
14 treatment or topical antimicrobial treatment? That may be
15 an endpoint as well.

16 DR. SHERIDAN: That is a good point because if you
17 think someone has burn wound infection, this is a very
18 dangerous thing and systemic treatment is instituted for
19 that, systemic and often surgical at the same time.

20 DR. GREENHALGH: But I think that a fairly large
21 group of us, or at least a group of one --

22 [Laughter]

23 -- that doesn't equate treatment with antibiotics
24 as being the equivalent of infection. I mean, there are a

1 lot of patients, particularly if they are very sick, who may
2 be presumed to be infected and get treated and it turns out
3 to be something else. At least in many of the antibiotic
4 trials we have participated in, in the past, the decision to
5 use antibiotics has never been a definition of infection.

6 DR. MCGUIRE: So you would ask for criteria for
7 systemic antibiotic drugs?

8 DR. GREENHALGH: Well, criteria for diagnosis of
9 infection.

10 DR. MCGUIRE: Right. The second part of item 2
11 under topic 5: Please indicate how wound infection might be
12 evaluated and monitored, e.g., clinical, microbiological,
13 and histological assessments, and now we are dealing with as
14 well as monitoring systemic effects, wound healing and graft
15 take. Was it systemic effects of the treatment, the injury?
16 What do you have in mind?

17 DR. WITTEN: Systemic effects of the wound
18 infection, for example sepsis.

19 DR. BERGFELD: Such as blood cultures perhaps?

20 DR. MCGUIRE: You really want to know how a wound
21 infection influences the patient systemically as well as how
22 it influences wound healing and graft take.

23 DR. WITTEN: Or how you might monitor that; how
24 you can evaluate that.

1 DR. GREENHALGH: It is a difficult thing to do. We
2 do tend to treat people aggressively with signs of sepsis.
3 Now the source of that sepsis is often defined. We will,
4 for instance, look at increase in fluid requirements,
5 dropping platelet counts, intolerance of feeding. There are
6 a lot of signs we use as indicators of sepsis. Now, the
7 initial source of that sepsis is difficult, and the wound as
8 a source is very infrequent. We used to get invasive
9 Pseudomonas. We get it rarely now but the wound causing
10 systemic sepsis is very uncommon. So, finding the specific
11 source can be difficult. A lot of times it is pneumonia; a
12 lot of times we don't find what it is. Even at autopsy we
13 don't find out what killed the patient.

14 DR. YURT: One of the things to consider is that
15 any of these patients that have large burns, probably larger
16 than 30%, have basically what is considered systemic
17 inflammatory response. So, they frequently will have fever.
18 They will have elevated white counts. They will be
19 hypermetabolic, and so forth. So, they meet many of the
20 criteria for systemic "sepsis" that we usually think about
21 so it really is a matter of being extremely aggressive in
22 evaluating them, and if you do get down to the question of
23 wound versus other sources, it really is a matter of being
24 aggressive in ruling out everything else -- pneumonia, line

1 sepsis and coming down frequently to a diagnosis of
2 exclusion unless the wound still has enough residual eschar
3 and so forth that you can make a biopsy-based diagnosis.

4 DR. GOODWIN: I was just going to say what Dr.
5 Yurt said, that it is very difficult, if it is possible at
6 all, to separate the inflammatory response to the wound from
7 what non-soft tissue injury people consider signs of sepsis.
8 That is one of the large problems. We have all had patients
9 with cardiac outputs of 15 or 20 and everything else. It
10 has absolutely no relationship to a bacterial origin or
11 microbial origin.

12 DR. BERGFELD: It seems then that what you have
13 all said is that in the clinical studies you wouldn't
14 exclude anyone if they were on antibiotics. The only one
15 question I have is on antibiotic therapy, since you have run
16 other clinical studies, is there an enhanced healing for
17 individuals who are on antibiotics? So, if there is not,
18 then that question is mute whether they have sepsis or not.
19 The focus should be the wounds, the cutaneous wounds.

20 DR. MCGUIRE: If there is no further discussion on
21 that point --

22 DR. MAYHALL: I just wanted to summarize. We were
23 talking about a crisp endpoint of treatment of burn wound
24 infection. One of the problems with that, of course, with

1 being unable to diagnose it is making sure we have burn
2 wound infection to start with because the patients are
3 likely to have some other possibilities for other
4 inflammatory appearance. The fever and the white count
5 might be the inflammatory response; it might be line
6 infection; pneumonia; infection at some site from some other
7 trauma sustained at the same time they got their burn wound;
8 it might be the burn wound. So, the problem is using that
9 endpoint of treated burn wound infection that you have to
10 make sure they had a burn wound infection to start with.

11 DR. MCGUIRE: I think we are set on that point.
12 Thank you.

13 There are a number of subjective methods for
14 evaluating scarring. For example, the Vancouver Burn Scar
15 Assessment method measures pigmentation, vascularity,
16 pliability and scar height. Please describe the methods of
17 scar assessment that may be employed in clinical trials.
18 Please discuss the value and limitations of each method.

19 Who is first?

20 MR. RICHARD: I will begin. At this point there
21 is no good way of measuring burn scars in terms of it,
22 again, being standard. Vancouver Burn Scar Assessment came
23 out in 1990, and since that publication it has sort of been
24 used across the board. But it is highly subjective and

1 there is a lot of variability in terms of looking at
2 hypertrophic scars, which is what it addresses.

3 There are some mechanical means of looking at
4 scar. There are elastometers; there are tonometers; there
5 are bioelectric impedance devices which are more
6 quantitative and more objective. However, those sorts of
7 devices have been used in isolated instances and have not
8 made their way into the burn area extensively, for what
9 reason I am uncertain of.

10 But what is interesting about Vancouver, and there
11 was a recent study that came out in The Journal of Burn Care
12 and Rehabilitation just this year from another burn center,
13 well-known burn center, looking at another way of looking at
14 burn scars, and the bottom line of both of these studies, I
15 think, in terms of beginning points is that even though they
16 are subjective, in comparing the two studies they all had
17 very high inter-and intra-rater reliability in terms of
18 people, i.e., the therapist, doing the studies, looking at
19 the scars.

20 Looking at the two studies also, I think it showed
21 that regardless of what was used in terms of evaluating a
22 scar, as long as it was looked at in the same fashion and
23 the same manner between all those individuals looking at
24 those scars, then you at least have a starting point.

1 DR. SHERIDAN: We have spent a lot of time with
2 this. This is a really difficult problem, as Reg alluded
3 to, also complicated by the fact that there is a natural
4 evolution of these scars, whereby if you take the same scar
5 and look at it, you know, one year later it looks a lot
6 different. So, what we have done is to look at the delta
7 between the study site and a matched control at the
8 beginning and followed the change. In other words, we have
9 used the Vancouver Scar score and we have also used a
10 subjective cosmetic grading system based on photographs by
11 third parties, acknowledging the weaknesses there, and then
12 we have looked at the delta between the control study site
13 which is following its natural history, many times getting
14 better anyway, and the study site with whatever
15 intervention, and I think that has worked for us. I think
16 it is really key to have a very well-defined control in any
17 kind of study of scar.

18 DR. GOODWIN: I actually think that in many
19 respects that is sort of a cop out. The definite endpoint
20 that I think you have to look at is when the scar reaches
21 its final appearance. In some patients, particularly
22 children, this may take more than five years. If you look
23 at any point in between you are not going to be getting an
24 accurate picture of the ultimate effect of these materials.

1 Most of us would not get reimbursed for more than three or
2 four visits, and they are all shot within the first three or
3 four months. So, with managed care you are not going to
4 have these long-term follow-ups.

5 DR. MCGUIRE: Well, that may be true and managed
6 care is chasing all of us around, of course, but if we
7 design trials there would have to be support for the trials.

8 DR. GOODWIN: But if you are going to design a
9 trial to assess the effect of treatment on scarring, you
10 have to wait until the scar reaches its final appearance,
11 otherwise you have just sort of inventing a study that is
12 never going to answer the question.

13 DR. MCGUIRE: And the other part of that is who
14 supports the clinical visits --

15 DR. GOODWIN: You bet you.

16 DR. MCGUIRE: -- and that would have to be built
17 into the study.

18 DR. GOODWIN: You guys want all of this. So,
19 somebody is going to have to come up with the money to do
20 it, and it is going to be very, very expensive.

21 DR. GREENHALGH: I have a couple of points. Just
22 like the wound healing issue, it depends on where you look
23 and how much -- I am surprised Reg didn't mention it -- how
24 much therapy they get; how much pressure garments they have.

1 For instance, if you do a nice graft, the most beautiful
2 graft in the world, if you don't follow-up with their
3 therapy they can have a lousy result. So, there are a lot
4 of variations on what you do to treat the scar and how it
5 turns out at the end that you have to include as part of the
6 evaluation.

7 But, again to support what Reg said, these systems
8 have worked somewhat between the different agencies or
9 different studies and they have worked okay as far as inter-
10 discipline variability.

11 MS. COHEN: I am going to ask a naive question.
12 What about the emotional havoc that is wrought by people who
13 have been burned? Does healing have anything to do with a
14 positive outlook, or receiving therapy, or whatever would be
15 appropriate for people who go through this terrible trauma?

16 DR. GREENHALGH: We have done outcome studies, and
17 that is a big push for the American Burn Association. You
18 know, if you do it right the first time the cosmetic results
19 can be fairly good. Children go back to school; adults go
20 back to work. And, there are a lot of studies on the
21 emotional aspects. The Galveston people have done studies
22 on massive burns, and they have good acceptance of their
23 injuries. So they have been looked at.

24 DR. MCCAULEY: I think from the standpoint of

1 esthetics and function, you can actually break these groups
2 into two areas -- those that have burn scars that are easily
3 hidden versus those that don't. Obviously, we are talking
4 about patients with facial burns and disfigurement, and I
5 think psychologically they are worse than those that don't
6 have burns of the face but have burns of the truncal
7 regions, hands and arms and legs. So, there is a big
8 difference from that standpoint. But I think in children
9 overwhelmingly their psychosocial status is surprisingly
10 good.

11 I do want to make one comment about the burn
12 assessment of scarring. That is, we really don't have a
13 very good method to assess scarring. It is clear that no
14 matter what we do, we are taking a static measuring point in
15 a very dynamic process, and the endpoint of that process is
16 not always very clearly defined. So, we have to just accept
17 that as a weakness in any kind of study that is being
18 designed.

19 There are a number of things that have come out
20 recently which Reginald has mentioned, the tonometry, the
21 ultrasound and some people are even starting to look at the
22 laser Doppler in terms of blood flow studies in comparison
23 to blood flow in normal tissue. But, again, these things
24 are just at the early stage of evaluation.

1 MS. CARROUGHER: I just would like to underscore
2 what was said about the different scoring systems. Because
3 the document we were given mentioned the Vancouver Scar
4 scale, I just would ask that the committee look at other
5 scales that are out there, just to help them determine which
6 may be the most appropriate given the study design.

7 Also, one issue that Ms. Cohen brought up about
8 how people looked at outcomes as far as emotional, there are
9 many studies that are ongoing around different burn centers,
10 and one in particular at the University of Washington is
11 looking at pain that is experienced during inpatient, and
12 then looking at long-term follow-up as far as emotional
13 recovery two years post-discharge from the hospital.

14 DR. MCGUIRE: So, it sounds like the psychosocial
15 evaluations are ongoing and that the tools needed to measure
16 objectively scarring and scarring outcomes are in progress,
17 early progress. Is that right? Does the Agency need
18 anything else on this point?

19 DR. WITTEN: No, thank you.

20 **Topic 6: Efficacy Endpoints**

21 DR. MCGUIRE: Let's go to topic 6, efficacy
22 endpoints. There are three paragraphs which you may read
23 and then we will go to specific issues.

24 DR. ROSENBERG: If anybody is looking for

1 objective evaluators of outcomes that were suggested before,
2 we have a number of length of stay ladies down at our place
3 that could do very well with that, and I would be glad to
4 give you their names. I think they are highly qualified for
5 walking in and looking at people and saying this one is
6 done. They have had the training for it. So, it might not
7 be so impossible to find such people in studies. Every
8 institution has them.

9 DR. MCGUIRE: Well, that would be very important.
10 Are we through with our three paragraphs here? Please
11 discuss the following issues. Regarding wound closure,
12 please discuss how complete burn wound closure may be
13 defined and measured in partial thickness burns.

14 Dr. Witten, is there something embedded in that
15 question that I am missing?

16 DR. DURFOR: I think you could interpret the word
17 closure. What we probably meant was healed. So, when you
18 are looking at a wound, a partial thickness wound, when is
19 it judged as healed, once again looking for an objective
20 endpoint?

21 DR. MCGUIRE: Okay.

22 MR. RICHARD: I think using the word closure is
23 also important in this instance because there are two
24 different issues. One is wound closure, when the wound

1 actually fills in with some tissue. But then, as I think
2 Dr. Goodwin mentioned, you know, burn scar maturation can
3 take up to three to five years, which we would then consider
4 clinically healed. So, I think there are two distinct
5 issues there and I am not sure exactly which one you really
6 want to address.

7 DR. DURFOR: I think we would welcome comment on
8 both.

9 DR. MCGUIRE: They also need information on
10 durability of closure. That is, you are moving toward a
11 point and then once you have closure, we have to have a
12 second look for durability.

13 DR. GOODWIN: Practically, I am not sure how that
14 is done. In practical terms, I think we are thinking about
15 closure of the wound, that is, coverage of that wound with a
16 stable epithelium.

17 DR. MCGUIRE: That is right, but I think the
18 Agency also is interested in some measurements of
19 durability. They are nodding yes.

20 DR. SHERIDAN: What we use is just the day you
21 take the dressing off, let the person go around with no
22 dressing and that is a durably healed wound.

23 DR. GREENHALGH: I have some patients take the
24 dressing off the first day and it dries up. So, it is not a

1 great indication. I agree with Dr. Goodwin. When you re-
2 epithelialize, that is when you have a functional barrier
3 from water loss and bacterial invasion. So, that is a
4 functional change. We talked about that before, is it 90%
5 or 95%? There are objective measures, such as surface
6 electrocapacitance. There are evaporative measures and
7 things like that, that we kind of mentioned earlier. But I
8 think we all look if it is re-epithelialized or not. You
9 pointed out earlier that there are some difficulties with
10 that. There haven't been any good studies at all. We do
11 look at how much they reblister. For some of the cultured
12 keratinocytes there is blistering ongoing for months, and no
13 one has been able to quantify that but I think that is an
14 issue that we all deal with, and I don't know if anyone has
15 ever tried to quantify it.

16 DR. YURT: One way to look at it is to break it
17 out from the durability standpoint, if you are talking about
18 what the dermis contributes as well as what the epidermis
19 contributes. We are just talking about partial thickness
20 burns here. I think durability is more of a question and a
21 different problem in the deeper burn, but in partial
22 thickness it usually ultimately is fairly durable. It is
23 not as much of a question as in full thickness.

24 DR. BERGFELD: As a pathologist and also a

1 dermatologist, I can agree with everything that has been
2 said regarding healed. Certainly, that can be assessed both
3 clinically as well as histologically. The durability and
4 the strength of the tissue, however, is a major problem in
5 assessment and that takes quite a while to be "durable,"
6 consistent with normal skin, up to a year or two.

7 However, the statement regarding scarring, a
8 scarred wound is a healed wound. A scarred wound is an
9 over-response in healing and it would be an adverse sequela
10 of the injury to the tissue and the fibroblastic response,
11 as well as some other things. So, I am not sure where scar
12 falls into the wound closure or the wound healing. In my
13 mind, it doesn't. It is sequelae of the injury, and it is
14 an over-response to the injury. The wound has been healed
15 for some time.

16 DR. GREENHALGH: Well, you have to be careful
17 because you are saying it is re-epithelialized and it
18 functions as a barrier to water loss --

19 DR. BERGFELD: No --

20 DR. GREENHALGH: -- but if you look at any graft,
21 and we all know that it looks good at five days, it gets
22 thicker and it goes through months of changes where it gets
23 redder, scars more, thicker, then it fades out over the next
24 several months. So, you may say, yes, functional as far as

1 water loss but as far as durability and mobility, until that
2 redness has gone away and has faded --

3 DR. BERGFELD: No, we agree. We agree on that. I
4 am saying that durability and strength of that wound is the
5 issue, at least as I see it, because if you were to biopsy
6 these, these are not strong wounds until they are out to a
7 year or two because the skin is easily separated; it is
8 easily reinjured; it is easily made non-viable again by a
9 lot of different things.

10 DR. GREENHALGH: What we do look at is
11 functionality. Are they able to wear their shoes again?
12 Are they able to wear clothes? Do they not break down with
13 mild trauma? That is what we really use but quantifying
14 that is pretty difficult.

15 DR. MCGUIRE: So, those functional markers would
16 be useful in assessment of durability. Other comments?

17 DR. MCCAULEY: Yes, I think you have to separate
18 out wound closure from wound maturation. I think those are
19 two separate issues.

20 DR. MCGUIRE: Yes. And, we could probably split
21 this out into a number of different phases if we decided to
22 go that way but the first milestone would be re-
23 epithelialization. Then you have remodeling and that goes
24 on forever, forever being more than a year. Are there other

1 comments?

2 DR. MARZELLA: I would also like to add a slightly
3 different definition to durability, and that is from the
4 standpoint of what the Agency is interested in, and that
5 often is durability of clinical benefit, however defined.
6 When is optimal durable clinical benefit reached?

7 DR. GOODWIN: I would just like to add a comment
8 to that. Many of our current problems in treating burn
9 patients is taking the concept of coming to some place where
10 we can say we see a definable benefit. Burns are a chronic
11 disease of which the hospitalization is just a tiny, usually
12 the easiest, part. What happens after that is the most
13 important part. If you are going to find something that you
14 can measure, say, as a change it may have absolutely no
15 relevance to this patient's disease process. There are
16 periods during the maturation of that burn scar where things
17 look very good and if you wait long enough they look bad for
18 a while. If you wait even longer they look good again.

19 DR. MCGUIRE: Thanks for the comment. I think
20 everyone agrees with that.

21 DR. DURFOR: Just a follow-up question if I might,
22 and that is if the concept of what a closed or a healed
23 partial thickness wound is sufficiently well understood, is
24 there a need for an independent evaluator, or is it

1 something that the treating physician can do in an objective
2 manner?

3 DR. MCGUIRE: We touched on that a little bit.

4 Does anyone want to comment? Dr. Sheridan?

5 DR. SHERIDAN: I can tell you that my own practice
6 is with lots of kids with scald burns. When the thing is
7 durably healed I tell mom let him run around without a
8 dressing; that is fine. And that day, to me, is a
9 meaningful, very hard to obscure endpoint. That is not
10 necessarily the day that it is 95% re-epithelialized because
11 frequently that 95% re-epithelialization is very fragile,
12 and it is subject to rubbing off on the rug. So it is
13 obviously a very difficult endpoint, but within the practice
14 pattern of a specific unit there are certain endpoints that
15 are very functionally based. In my practice that is the day
16 I tell mom no dressing. That is a very hard endpoint in my
17 unique practice.

18 MS. CARROUGHER: Is the question should a non-
19 biased investigator be making that determination, or the
20 investigators involved in the protocol be making that
21 determination? Am I correct?

22 DR. DURFOR: The question is simply does it need
23 to be done by a masked observer to make sure that it is an
24 objective hard endpoint.

1 DR. GREENHALGH: What you are talking about are
2 outcome studies which we all need to do. What is probably
3 more important is does the person return to work at a
4 certain time than how does it look to some other observer?
5 Or, can they go back to school? Those are the outcome
6 studies we all realize are real important, and it is hard to
7 do those in a prospective fashion. But, you know, can a
8 carpenter go back and put a wall up on a house or not, or
9 does he have to stay off work for three months? That is a
10 lot more worth to society.

11 DR. WITTEN: I would certainly agree with that but
12 I am just interested to know whether any of you, perhaps Dr.
13 Sheridan, could characterize what elements would go into
14 telling, let's say, the mom that it is time for the kid to
15 take the dressing off and run around. In other words, if it
16 is not 95% re-epithelialization what kinds of things would
17 you look for to go into that decision?

18 DR. SHERIDAN: I think everybody here that takes
19 care of burns knows when a wound looks durably healed and
20 when it is very fragile, barely re-epithelialized. It is a
21 subjective thing but it is consistently subjective, I
22 suspect, within individual practices.

23 As far as the blinded examiner, I think that if
24 you are going to have any kind of a subjective endpoint,

1 such as is this epithelium 95% of this wound or is this
2 fibrinous exudate with non-viable cells causing an
3 opalescent appearance, I think you need a blinded examiner
4 for that.

5 DR. GREENHALGH: It is also not a clear endpoint
6 because even as they are healing we will have them doing
7 functional things. You may say, "all right, you can take
8 your dressing off but don't go out and play soccer because
9 if you are kicked you can rub that thing off." Then you can
10 say, "well, after three weeks you can go play soccer." Then
11 after that you can do other things. So, it is not clearly,
12 you know, at this point you can do everything you did
13 before.

14 DR. MCGUIRE: So, one could generate a series of
15 graded criteria, degrees of functionality. We are going to
16 discuss these points again under 1 (b) regarding grafts and
17 skin substitutes. What are acceptable criteria for defining
18 wound closure?

19 We have already discussed that, and I think we
20 agreed that we have a pretty good handle on it. However, it
21 is difficult sometimes to tell if there has been good
22 migration. Yes?

23 DR. GREENHALGH: I would just make one comment
24 about that. A lot of the studies with the skin substitutes

1 would say oh, we have complete graft take at four weeks, or
2 whatever. You have to be careful in that, you know, we look
3 at a graft take at five days and that is different than if
4 you look at four weeks. So, time has to be consistent. For
5 instance, if you have a graft take 95% at five days, well,
6 it will re-epithelialize. At four weeks almost anything
7 would be 100% healed. So, you have to make sure you have a
8 consistent time that is acceptable. We look at graft take
9 at five days to seven days as opposed to weeks later. At
10 that point, things are contracted in and there are a lot of
11 other variables that have contributed to the closure.

12 DR. MCGUIRE: Are you talking about re-
13 epithelialization of the interstices of a split thickness
14 skin graft?

15 DR. GREENHALGH: No, I am talking about if you put
16 a skin substitute on a wound versus an autologous graft, and
17 you look at it and it is all there in an autologous graft at
18 five days, but you look at the skin substitute and it is 50%
19 there. Well, if you wait until day 28 the skin substitute
20 will also have healed at that point. Yet, they say they are
21 equal because at four weeks they both cover the wound. So,
22 you have to be careful that you have a specific time point
23 that you look at that is acceptable. We usually look at
24 graft take at about five to seven days, whereas some of the

1 studies have reported three to four weeks.

2 DR. YURT: I think this opens up a whole other
3 area as well. If you take a silastic membrane and put it
4 over the wound and it closes it, then you have a certain
5 degree of wound closure. For some patients that is an
6 important thing and something that we would do to get
7 temporary wound closure. So, we are now differentiating
8 also between temporary wound closure and permanent wound
9 closure.

10 DR. MCGUIRE: And there are some special subsets
11 of this clinical scenario in which the immunosuppressed burn
12 patient accepts an allograft for a limited period of time,
13 and that is closure but it is not permanent closure. It is
14 permanent until he decides to reject it unless you do
15 something in the interim.

16 These next three items, what outcomes could be
17 used to define clinical benefit, e.g., graft durability; how
18 can the take of grafts or skin substitutes be evaluated; and
19 how long should a grafted wound be monitored to assess the
20 durability of closure -- these are quite closely related and
21 I would like to deal with them together, if we could. Would
22 anyone care to address one of these? Dr. Drake?

23 DR. DRAKE: Maybe this is already being done but I
24 have heard several of the burn surgeons today comment

1 repetitively on pain. Sometimes these dressings are used
2 for pain. So clearly under number (ii), what outcomes could
3 be used to define clinical benefit in addition to durability
4 and function -- and I have kind of gotten into quality of
5 life studies myself; I am kind of interested in it and I
6 think pain is a major factor and I think we often underrate
7 it, and underestimate how disabling this is for the patient.
8 So, if you can get some pain relief, I think that is a very
9 important parameter.

10 DR. MCGUIRE: I think Dr. Sheridan mentioned
11 earlier monitoring use of morphine or analgesics. Someone
12 mentioned that earlier.

13 DR. DRAKE: Well, it is not so much that; it is
14 can you get pain relief from some of the dressings or some
15 of the therapeutic agents or devices, or whatever you are
16 studying? Does it provide pain relief? It may not speed up
17 the healing but if there is pain relief, I think that is
18 almost equally important during the healing process.

19 DR. GREENHALGH: Pain is important but you don't
20 want to concentrate totally on pain and then have a non-
21 functional result a year later.

22 DR. DRAKE: I wasn't saying that. I am just
23 saying I think pain ought to be one -- say, somebody comes
24 up with a new dressing that may not actually speed up the

1 wound healing but it gives them tremendous pain relief, I
2 think that is an important thing to monitor.

3 DR. GREENHALGH: Absolutely. We agree with that.

4 DR. RICHARD: And there is a host of scoring
5 systems that would be useful.

6 MS. CARROUGHER: I was just going to comment on
7 the pain issue since, at the University of Washington, that
8 is my primary focus. I would encourage the Agency, when
9 providing recommendations, that not just one measurement of
10 pain be considered but actually a whole host of measurements
11 of pain, i.e., worst pain, average pain. There is a lot of
12 information reported on the differences between kinds of
13 pain.

14 In addition, I would encourage that an element of
15 patient satisfaction as well with whatever dressing or
16 device is utilized be considered.

17 DR. GREENHALGH: I will address how long you
18 should monitor a grafted wound for durability. I think you
19 need at least a year. As Dr. Goodwin has talked about, you
20 want to see is if the redness has gone away. We use that a
21 lot of times. The other objective measure, or pseudo-
22 objective measure is when they get out of pressure garments
23 a lot of times. Those are a couple of things. But usually
24 when I have done studies I have wanted to follow them at

1 least a year to see, You don't want to put something on
2 that accelerates healing that a year from now causes
3 excessive scarring. So, I think it is important to follow
4 them fairly long term.

5 DR. MCGUIRE: That feeds on the previous item too,
6 which is how do you evaluate skin substitutes and grafts,
7 because some of the grafts are in forever and some of the
8 grafts are there temporarily. So, you can have a good
9 short-term outcome. Unless you do something else to deal
10 with that wound --

11 DR. GREENHALGH: Absolutely. The example is the
12 cultured keratinocytes alone which have been used for a long
13 time but the long-term results were not very good. So, now
14 even the people who promoted the cultured keratinocytes
15 agree you need a dermis also. So that is an example that
16 long-term follow-up is important. The take was okay but it
17 was the long-term problems that made the difference.

18 DR. MCGUIRE: Right.

19 DR. BERGFELD: May I ask a question? Are there
20 ways of measuring strength of a wound? Histologically, the
21 anchoring fibrils that hold the epidermis and dermis
22 together are absent for quite a long time. So there is a
23 shearing effect that is quite easily imposed.

24 DR. GREENHALGH: There are ways to do it. There

1 are ways to test how much strength it takes to clear a
2 blister. There are ways to do tensiometry on human skin,
3 but most of our patients don't want to get a new wound to
4 assess that. You know, they are making another wound. But
5 they have been tested. There are also devices for looking
6 at wound healing in people but they are all invasive, a lot
7 of these things are, looking at cellularity of implants.
8 Most of our patients don't want to go through that when they
9 are in the convalescent stage. They want to get on and back
10 to normal life.

11 DR. BERGFELD: How about color of wound, red
12 going to white?

13 DR. GREENHALGH: We do use that. That is part of
14 the Vancouver score. As I said, if the wound looks white we
15 usually kind of call that mature. It is not very objective
16 but it is what we use.

17 DR. BERGFELD: There are scales that can be
18 developed around color that could be meaningful.

19 DR. GREENHALGH: Right. It is difficult with the
20 pigment issues too.

21 DR. BERGFELD: We are talking red to white --

22 DR. MCCAULEY: Yes, but in patients of color that
23 sustain major burn injuries how are you going to evaluate
24 that?

1 DR. BERGFELD: That is a problem.

2 DR. GREENHALGH: And pigment differences are a big
3 problem.

4 DR. MCCAULEY: Right.

5 DR. DRAKE: At the Mass. General we have developed
6 a method for looking at color and skin, whether it is
7 pigmented or not, and we have actually validated it now in a
8 couple of studies and it has been published. But it is not
9 something that would be readily available because it is in a
10 machine we built there. But the answer is that the
11 technology is there to evaluate color even in heavily
12 pigmented skin, and we have it, we have validated it and
13 published it. But I do think that what you need is somebody
14 who is interested in making that instrument so that it is
15 widely available for clinical studies so that other people
16 can use this piece of equipment. But it is particularly
17 useful because we not only can measure erythema; we can
18 measure pigment too, and not invasively but just by putting
19 a probe on the skin and you get the measurement in a few
20 seconds. So, it has been used in a lot of studies, photo
21 damage studies, erythema and all kinds of things.

22 DR. BERGFELD: Does it also measure heat of the
23 wound?

24 DR. DRAKE: No, it doesn't. It doesn't measure

1 heat. We have studied the temperature to make sure that the
2 temperature didn't influence the results, and the
3 temperature of the skin does not influence the results of
4 the data.

5 DR. MCGUIRE: Mrs. Cohen, you have a question?

6 MS. COHEN: Yes. I want to ask Gretchen a
7 question, if I could, about the role of the nurse. Since
8 the nursing staff really spends more time with the patients
9 than anybody else, what do you envision your role is, and
10 are nurses trained to recognize when there is a change in
11 the wound to contact the physician?

12 MS. CARROUGHER: I think in recognized burn
13 centers the answer to your last question, are nurses trained
14 to recognize changes that are visible in the wound, and do
15 they know when to contact a physician, my whole-hearted
16 answer is yes.

17 Although I would agree with your comment that
18 nurses spend the most amount of the hours per day with the
19 patient, I think in most burn centers around the country
20 physicians and surgeons are very actively involved in
21 assessing people's wounds on a day-by-day basis. For
22 example, at the three major burn centers I have worked at,
23 rounds where wounds are visualized are a daily, if not twice
24 daily, occurrence with a given patient. Those occur after

1 hydrotherapy, after wound cleansing so that the wound can be
2 examined without any kind of dressing over the top.

3 So, my answer is yes, nurses and therapists are
4 equally good and trained in identifying problems that
5 require physician or surgical input, but equally as much,
6 surgeons are actively involved in the day-to-day management
7 and care of the burn wound.

8 DR. SHERIDAN: I think that is a great point
9 because the nurses really are right there. We have tried to
10 incorporate some of their, admittedly subjective, feelings
11 about wound pain and difficulty of dressing changes as
12 endpoints, and I think those would be reasonable endpoints
13 if there is a dressing that is supposed to decrease pain,
14 especially if it is on a small child that can't do the
15 recognized scale for pain, to get the nurse's impression of
16 this on a scoring system is entirely reasonable as an
17 endpoint.

18 DR. MCGUIRE: We have other study endpoints to
19 consider, and I think we can deal perhaps with one of those
20 before we break. We are now under number 2(a): In addition
21 to measuring wound healing, what are other clinically
22 meaningful endpoints and how might they be quantitated?
23 Please consider the following types of products -- debriding
24 agents. We spoke a little bit about proteolytic agents

1 earlier and their uses.

2 DR. HUNT: Well, the enzymes, I mean, it was a
3 gross assessment of the wound, and it is difficult in this
4 kind of a scenario with enzymes to have an adjacent area
5 that does not have the enzyme and then the enzyme because,
6 in the same dressing, they sort of melt together. So, that
7 is a problem that anyone has to deal with when they are
8 evaluating any kind of an enzymatic debriding agent. You
9 have to get two areas that are comparable. You have heard
10 all morning how difficult it may be. But it was purely
11 grossly looking and seeing by the surgeon, assessing it, and
12 by photographs -- has it debrided as much as it can? How
13 much difference was there from one day to the next? And, it
14 was very subjective. Very.

15 DR. MCGUIRE: I guess a measure of the success of
16 enzymes would be how universally they are used and under
17 what conditions. I would be interested in how the burn
18 surgeons are using debriding enzymes now. Yes, Dr. Goodwin?

19 DR. GOODWIN: It is hard to know. I think most of
20 us consider these agents dangerous, at least on big burns.
21 There are case series reports that it increases the
22 incidence of burn wound infection. In addition, their use
23 can be associated with fairly massive blood loss of the
24 debrided wound, requiring transfusion and exposure to agents

1 and so forth. At least in my experience, which I admit is
2 very limited, these agents will eat away a lot of the dead
3 tissue, but there is always a layer that is left that still
4 requires some addition excision to where it can be grafted.

5 DR. WITTEN: If I may comment on the question?

6 DR. MCGUIRE: Yes.

7 DR. WITTEN: A debriding agent I think could be
8 taken more generally all products that might debride, like
9 hydrotherapy. I think our question isn't so much about the
10 product but if debridement is the endpoint, how that might
11 be assessed.

12 DR. GREENHALGH: A lot of these agents were
13 designed in the past where the treatment was different,
14 where you would wait for the natural separation of the
15 eschar and this would accelerate that rate. Most of us now
16 use the old-fashioned steel method that cuts it off, and it
17 works very well so you don't have to wait for these things.
18 So, it is hard to have an endpoint for them.

19 The other issue is that in a lot of the studies
20 with enzymatic agents, they will say that it looks like the
21 scab has come off, which it hasn't, which doesn't mean much.
22 It still has to heal. You have to look at the rate of
23 healing. Then some of the studies suggest that even though
24 you have used an enzymatic agent, as Dr. Goodwin said, you

1 still have to excise it anyway. The grafts don't take just
2 on those enzymatically debrided areas. So, if we are in the
3 era now where we get rid of that burden of wound by cutting
4 it off and putting a graft on it, that is not as important.

5 DR. YURT: I think the bottom line with
6 debridement is whether the wound, once it is debrided, is
7 ready for autografting. For example, we may have some
8 intermediates. If we think it is ready but we are not
9 absolutely sure, we may take an intermediate step and put an
10 allograft on to test it and then, once we are sure, we can
11 go to the second step and use autograft. But I think that
12 is the bottom line of debridement, whether it is going to
13 take a graft or not.

14 DR. MCGUIRE: You said that in sort of an
15 abbreviated way. I don't know if people who don't work with
16 burns understand that the allograft is used to identify a
17 wound that is ready to accept another kind of graft so you
18 don't waste the autologous graft on a wound that is not
19 ready, and the wound is not ready either because it is
20 infected or because there is too much fibrin on it, or some
21 such thing.

22 DR. YURT: Right. I don't use enzymatic agents
23 very much, but there may be some specific reasons for using
24 different debridement procedures. For example, if you are

1 close to viable bone or tendon that you are a little bit
2 concerned you might injure surgically, you might delay a
3 little bit in the surgical approach and, in that case, maybe
4 use another agent for debriding while waiting for things to
5 become clearer.

6 MS. CARROUGHER: In addition to the time from,
7 say, injury to the time you have determined that it is okay
8 to take them to surgery and put a graft on, other study
9 endpoints I would like to advocate are, again, pain
10 intensity -- things that we are concerned about are maybe
11 the pain intensity on application or the procedural pain
12 that the patient experiences but, again, the resting or
13 background pain that occurs when the patient is not having
14 an active procedure; also, possibly the impact on
15 surrounding intact tissue, and that is particularly relevant
16 for enzymatic debridement agents that might impact on intact
17 skin next to the injured area.

18 DR. MCGUIRE: I think that it is time to take a
19 break and we will be here at 1:30.

20 [Whereupon, at 12:30 p.m., the proceedings were
21 recessed, to be resumed at 1:30 p.m.]

1 AFTERNOON SESSION

2 DR. MCGUIRE: We are working from the draft from
3 the Agency. Question 2 is regarding other study endpoints:
4 (a) In addition to measuring wound healing, what are other
5 clinically meaningful endpoints and how might they be
6 quantitated? Please consider the following types of
7 products.

8 We talked about debriding agents, enzymatic
9 agents, and now we are considering topical analgesic agents.
10 Would anyone care to address that?

11 MS. CARROUGHER: Dr. Sheridan alluded to total
12 opiate use like on a 24-hour basis, which can be calculated
13 in opioid equivalence, and I would just include that as one
14 endpoint.

15 DR. MCGUIRE: That is correct and that is
16 important, and that is one endpoint. The Agency asked
17 specifically about topical analgesics.

18 DR. WITTEN: To clarify, with use of topical
19 analgesic agents what other opiate use the patient is
20 requiring to control pain as well could be another study
21 endpoint.

22 DR. ORKIN: Are you on number (ii) or (iii)?

23 DR. MCGUIRE: I am on question 2 regarding other
24 study endpoints, item (a)(ii). We are talking about topical

1 analgesic agents.

2 Does anyone use topical analgesics?

3 DR. HUNT: At the present time, I don't think so,
4 or at least I haven't encountered any. Certainly, one of
5 the problems is absorption. For large surface areas
6 absorption is going to be important even if the
7 concentration is low. With other things that are put on the
8 wound, if you combine it how does it interface with other
9 agents that may be on there, such as antimicrobial control?
10 Are you going to use it just before dressing changes? You
11 can't because they have a dressing on. So, I think they may
12 work for small burns. The application for large burns, I am
13 not sure what place they would have. But, certainly, the
14 toxicity is important.

15 They are interested in wound healing and
16 meaningful endpoints, but I think a lot of work would have
17 to go into realizing that the surface area of the burn
18 absorbs just everything and the toxicity is a major concern.
19 Again, this may be very short-lived because it will be
20 absorbed so fast.

21 DR. GOODWIN: I can just echo that. I don't think
22 any of us use it because of at least the anecdotal reports
23 of deaths from overdosing the patients that get it through
24 absorption through the wound.

1 DR. MCGUIRE: Yes, I think what is emerging is
2 that anything you put on the donor site is absorbed, and if
3 you have a fresh wound or if you have debrided a wound then
4 everything you put on that site is absorbed. So, the major
5 drawback of topical analgesia is absorption.

6 I think that is probably it for topical analgesic
7 agents. Topical antimicrobial agents and other products --

8 DR. GOODWIN: Before you go on, there are people
9 working with ways to manipulate that, particularly putting
10 some of these analgesic in liposomes and then putting them
11 on surfaces. There may be a solution or a reason to use
12 topical analgesics in the future.

13 DR. MCGUIRE: And you emphasize the fact that
14 delivery systems need to be designed so you don't have
15 systemic absorption.

16 DR. BERGFELD: Could I ask a question about that?
17 Is there any use of topical analgesics to debride the
18 wounds? I mean, just for pain control just for debriding?

19 DR. MCGUIRE: Would any of the surgeons care to
20 respond to that? Do you employ topical analgesia in
21 debriding a wound?

22 [No response]

23 I think the answer is no.

24 DR. GREENHALGH: I have on rare occasions used

1 some Lidocaine, but they have to be pretty small surfaces.

2 DR. MCGUIRE: Okay. Dr. Orkin?

3 DR. ORKIN: I asked some of the surgeons at the
4 luncheon break this question but I thought it might be well
5 to mention it to the group. That is, if they use Batroban,
6 mycopirocin, on the burns and so forth.

7 DR. MCGUIRE: And the answer was? Dr. Goodwin?

8 DR. GOODWIN: We have used it but primarily on
9 small open areas in burns that are otherwise healed. We
10 don't use it as a primary antibacterial.

11 DR. SHERIDAN: We use it, as Dr. Goodwin alludes
12 to, in small eroded areas that are growing Staph.

13 DR. MCGUIRE: Do any of the other surgeons wish to
14 comment on topical antimicrobials?

15 [No response]

16 It sounds like topical analgesia and topical
17 antimicrobials are not a central focus in dealing with these
18 wounds.

19 DR. GOODWIN: I think topical antimicrobials are
20 one of the mainstays of total burn care, at least in
21 patients with big burns. Just about everybody uses
22 Silvadine or Sulfamylon, or something of that sort.

23 DR. SHERIDAN: We very commonly use injection
24 long-acting anesthetics in freshly harvested donor sites and

1 end of case postoperative analgesia, but that is all.

2 DR. MCGUIRE: So, you generate a bloc.

3 DR. SHERIDAN: A field bloc.

4 DR. MCGUIRE: Other products? What other
5 products?

6 DR. DURFOR: I would like to return to the topical
7 antimicrobials for a moment, and this harks back to our
8 discussion on how to define a wound site infection.
9 Previously we have talked about that in terms of looking at
10 graft loss or other clinically important issues, but if the
11 incidence is probably low enough, I would expect that you
12 might need a very large study. So, this question is related
13 to study endpoints and I was curious in terms, of when you
14 focus on the issue of topical antimicrobial agents and study
15 endpoints, what might be a good endpoint? What does this
16 group feel is a good sign of clinical benefit?

17 DR. MCGUIRE: Comments? Did you understand the
18 question from the Agency?

19 DR. GREENHALGH: Yes. I think it depends on what
20 you are looking at. You could look at graft take or the
21 incidence of graft infection. We use topicals to prevent
22 infection on grafts, solutions and things. We have looked
23 at whether there is some purulence under the graft. So,
24 those are some indicators for graft take.

1 I think it is harder to look at when you put a
2 topical on a wound, like Silvadine, prior to excising it.
3 But we do use the topicals, especially on the large burns,
4 to help prevent infections on grafts. Someone mentioned the
5 silver nitrate solution; there are GU irrigants; Sulfamylon
6 solutions that we use because most of the time we don't have
7 a problem but on a rare occasion you do get a wound
8 infection on the graft and you lose the entire graft or a
9 good portion of the graft, and that is disastrous for us.
10 The incidence is very low though, so you need large numbers.

11 DR. SIMMONS-O'BRIEN: I guess this kind of brings
12 us back to the discussion this morning. When you use an
13 antimicrobial agent prophylactically in the beginning, it
14 seems like it is serving two purposes: It is an
15 antimicrobial and, as well, the vehicle is providing a
16 barrier and it is also probably serving as an emollient.
17 So, I guess in a study it would be interesting to know
18 whether or not any of the surgeons do this. Is there any
19 point in time when it looks like the wound is on the right
20 path in that it is not at as high a risk for infection? Do
21 you ever stop the antimicrobial agent but continue to use
22 some sort of other vehicle as a barrier or just as an
23 emollient, or do you continue to use the antimicrobial agent
24 even though your concern is always one of infection but it

1 is more that you are providing moisture to the wound at that
2 time?

3 DR. GREENHALGH: Yes, especially with sheet
4 grafts, whole sheets of skin without the mesh. You look at
5 it in a few days and it is vascularized. A lot of times you
6 can take them out of the topicals and they will do fine.
7 Moisturizing the wound afterwards is a real important issue.
8 We change things to non-antimicrobial moisturizing agents
9 pretty routinely.

10 DR. MCGUIRE: so is it conceivable that the
11 transition from a topical antimicrobial to a topical
12 emollient would be an endpoint?

13 DR. GREENHALGH: It is an endpoint but it is
14 pretty arbitrary.

15 DR. MCCAULEY: I think if you look at from the
16 standpoint of a topical antimicrobial actually being used in
17 preparation for closure of a wound and then you switch over
18 to an emollient, then we are actually talking about the same
19 endpoint, which is the time you can actually put a graft on
20 it and have it take.

21 DR. MCGUIRE: Other comments?

22 DR. YURT: What we routinely do is we will switch,
23 but we don't switch until the wound is closed so that our
24 endpoint would be closure of the wound. We tend to continue

1 using some type of antimicrobial until the wound is closed.

2 DR. MILLER: On the issue of absorption, you use
3 Silvadine. Are you concerned about Silvadine's absorption
4 and neutropenia? I don't know about Sulfamylon and all of
5 these agents, but specifically Silvadine which is used
6 widely in burn patients?

7 DR. YURT: We were concerned enough that a number
8 of years ago we did a study to look at that, and found that
9 there was a physiologic neutropenia that occurs, as is
10 fairly well recognized, after major injury, no matter what.
11 Nevertheless, if we get a neutropenia below 1500 neutrophil
12 count, we will switch topicals out of sulfadiazine because
13 we are concerned about it. Nevertheless, if the neutrophil
14 count comes back up, we frequently put sulfadiazine back on.
15 It is not particularly logical but we are concerned when it
16 drops down. But I don't think the incidence is very high.

17 DR. MILLER: Have you ever seen a drop a second
18 time?

19 DR. YURT: No.

20 DR. GREENHALGH: I was kind of taught in my
21 fellowship tenure, and I have done it since, that you don't
22 look at the white count, don't worry about it. There have
23 been studies looking at absorption and I think there is some
24 absorption but there is debate whether the neutropenia is

1 the result of the Silvadine or just from the injury itself.

2 DR. MCGUIRE: Do you have other questions?

3 DR. MILLER: I just want to ask if there is
4 something magical about Silvadine, or is there something
5 special about it as opposed to some of the other emollients
6 or barrier agents? It seems to have been used for a long
7 time, and is there a specific reason?

8 DR. GREENHALGH: Silvadine, I think, was invented
9 more for preventing infection, preventing Pseudomonas
10 infection. I think it is used so much because it is easy to
11 apply. It is very comfortable -- a lot of reasons that are
12 probably not of value to the FDA, but kind of like it is
13 easy to use; it has been used for so long we might as well
14 keep on using it. It may not be the best agent.

15 DR. MCGUIRE: What Dr. Miller was asking -- well,
16 no, this is what I am asking, Silvadine has been around a
17 long time. It is entrenched. Is there any reason to
18 dislodge it with another product? The use of Silvadine is
19 almost reflexive in an injury situation. Yes, Dr. Sheridan?

20 DR. SHERIDAN: We don't use it very often. We use
21 other topicals but we do use it a lot on outpatients because
22 it is easy to use.

23 DR. ORKIN: My recollection is that Silvadine,
24 being sulfadiazine, has a relatively high incidence for

1 contact dermatitis. I have seen it a few times myself.

2 What is your experience with the dermatitis? Wilma, do you
3 have any experience?

4 DR. BERGFELD: We have used it a long time at the
5 Cleveland Clinic in all departments of surgery and internal
6 medicine, and it really has not been a major problem.

7 DR. GOODWIN: The package insert says 5%.

8 DR. MCGUIRE: I have no idea what the incidence is
9 of allergic contact dermatitis.

10 DR. HUNT: I would be surprised if anybody will
11 introduce a major topical agent. It is probably not good
12 enough to show that it is the "same as." We have one, we
13 don't need another "same as" unless they drop the price.

14 The way wound cultures are now and wound
15 infections, there isn't a lot of money out there to recoup
16 for large burns, and the small burns can be treated with a
17 number of agents. But I would be surprised if anything came
18 out unless all of a sudden our wounds change completely and
19 some different type of organisms appeared that are not
20 present now, because it is a very safe agent. It is
21 comfortable, as was said. One reason Sulfamylon was dropped
22 is because it is exquisitely painful on partial thickness
23 burns.

24 DR. MCGUIRE: Comments from the Agency?

1 [No response]

2 I am ready to go on to part (b), other study
3 endpoints. Please discuss how possible deleterious effects
4 on the burn wound could be assessed. For example, delayed
5 wound closure, reduced graft take, decreased durability,
6 increased pain, increased wound scarring, and an increased
7 incidence of infection.

8 I think we have discussed many of these issues.
9 Are there specific items here that you would like us to bear
10 down on?

11 DR. DURFOR: I think we have spent a lot of time
12 discussing this. I would offer just an opportunity for
13 other comment on any of the particular issues here that they
14 have not had a chance to comment on -- if there are other
15 measures that can be used in a clinical study with objective
16 data.

17 DR. MCGUIRE: I think the committee feels like
18 they have already dealt with that.

19 DR. ROSENBERG: Are there any other comments on
20 small burns?

21 DR. MCGUIRE: There are obviously lots of small
22 burns out there, and there are people buying products,
23 products dispensed over-the-counter and by prescription.
24 Are there any of them that are more worthwhile or less

1 worthwhile, or does it really matter?

2 DR. GREENHALGH: If you get a little burn on your
3 knee it is the same thing as if you scraped your knee
4 falling off a bike. People don't do anything really special
5 for a scrape on the leg. It will heal the same way for
6 these little superficial burns, and it probably does not
7 make that big a difference. If you keep it clean it will
8 probably be okay. A moist environment for healing is
9 better. But you could argue about what to put on it. You
10 know, we went around for years without putting anything on
11 them and they did fine.

12 DR. MCGUIRE: For acute radiation injury, for
13 trauma and for minor burns I use a moist environment and
14 occlusive dressing.

15 DR. BERGFELD: I would like to ask a question of
16 the surgeons regarding it doesn't make any difference of a
17 day or two. When you are talking about healing time and you
18 are talking about small, medium and then you are talking
19 about large areas, you must have in your mind, because of
20 these comments, what the healing times are which are
21 acceptable for each group. For the small ones it seems not
22 to be a problem, for whatever reason, but could you discuss
23 the medium sized, or however you describe those, and then
24 the more serious by area and depth? What is your

1 expectation of healing?

2 DR. GREENHALGH: Pretty much, if a burn has healed
3 in two to three weeks, the scar is acceptable. If it is not
4 healed in two to three weeks, then we assess the need for
5 grafting. But if it is a difference between seven and eight
6 days, it is not going to make any difference in the end, or
7 seven and nine probably.

8 DR. MCCAULEY: I think we have a little bit of
9 confusion in terms of the size of the burn versus the dept
10 of the burn. You can have a very large burn that is
11 superficial in nature that you don't need to do very much
12 to; and you can have a very small burn that is deep or
13 indeterminate in nature that you may have to make some
14 surgical decisions about. So, I think we are getting a
15 little mixed up here.

16 **Topic 7: Inclusion and Exclusion Criteria**

17 DR. MCGUIRE: Dr. McCauley, let me keep you going
18 for a few minutes. Topic 7 deals with inclusion and
19 exclusion criteria, and the following covariates may affect
20 wound healing and partial or full thickness burn patient
21 survival. One of the issues is TBSA burn and depth of burn
22 wounds, which you were beginning to address, if you would
23 like to continue.

24 DR. MCCAULEY: The issue that I see here is

1 related to number 1 in terms of the size of the burn that
2 you want to study. I think if we were to come up with X
3 percentage total body surface area burns for patients
4 included in a specific protocol, you want to at least have
5 burns that are significant but not burns that have a
6 significant mortality attached to them. So, you may have to
7 look at burns, I would say, somewhere between 20% and 25% in
8 terms of just total body surface area burns.

9 In terms of depth, as was mentioned before, most
10 of us don't have to make very much of a decision between
11 those burns which are superficial, and will heal within a
12 week, versus those that are full thickness and we know we
13 will have to excise.

14 So, the real area in question in terms of trying
15 to make a difference, in terms of patients' length of
16 hospital stay and esthetic appearance, will be those burns
17 which are indeterminate in nature. The problem that we have
18 is how to assess it. Right now the best method we have is
19 clinical. Even though most of us think we are pretty good
20 at it, I think most would agree, at least in the literature,
21 that we are not as good at it as we think. That is why you
22 have all of the technology coming into place in terms of how
23 you assess a patient that has a deep or partial thickness
24 burn or a medium partial thickness burn, and how do you make

1 that surgical decision as to whether to excise it or not
2 because you are not sure whether it is going to heal in
3 three weeks.

4 DR. MCGUIRE: Would anyone else like to respond to
5 that point of total body surface and depth? These are
6 obviously very important criteria for any studies that are
7 done.

8 I have a question for the surgeons. We are all
9 aware of the immunosuppression that occurs with burn injury.
10 I am not clear-minded on how large an injury that needs to
11 be in terms of area. I have seen some figures and I must
12 not remember them correctly because it seems to me like a
13 very small injury is immunosuppressive. Can someone tell me
14 about that? That will influence the potential use of skin
15 bank allograft.

16 DR. MCCAULEY: I can answer that a little bit. It
17 depends on what you call a small burn. We consider a small
18 burn a 20% burn. But in terms of equivalence that may be
19 worse than multiple gunshot wounds to the chest and abdomen
20 So, in terms of a 20% burn causing an immunologic response,
21 that is certainly a large enough injury to have some effect
22 on the immune system. Even parents of burned children have
23 immunologic changes. So, I think that is probably a little
24 too diffuse to use as any type of entry criteria.

1 DR. MCGUIRE: So, is there a lower limit in terms
2 of area? I mean, would a 10% burn result in
3 immunosuppression?

4 DR. MCCAULEY: I don't know.

5 DR. GREENHALGH: It depends on your test. A lot
6 of these things are done in mice. They do a little, tiny
7 burn on them and they show a change in t-cell subtypes and
8 things like that which, by a specific test, may be a
9 difference but is that something that makes a clinical
10 difference? That is the big question.

11 But I agree with Dr. McCauley that you are
12 talking, you know, starting around 20% is a good size to
13 really start worrying about those issues. Also, that is the
14 size that really is probably going to make an impact on our
15 care. Can you change the care by looking at that size of
16 20% to a 40% burn size?

17 DR. MCGUIRE: I probably didn't make my point
18 clear. While immunosuppression is viewed as something bad,
19 immunosuppression also permits you to use a skin bank
20 allograft.

21 DR. GREENHALGH: Yes.

22 DR. MCGUIRE: Are there other comments?

23 DR. HUNT: Yes, I think the larger the burn -- you
24 know, it is a sigmoid curve -- the larger the burn, the

1 greater the immunosuppression and the greater the metabolic
2 demand, the greater the incidence of infection. And 20% to
3 25% is when you start seeing immunosuppression, at least
4 laboratory-wise. Clinically, I am not sure that that is
5 where it fits in. But, yes, the large burns you can put a
6 homograft or an allograft on and it does stay on, but it
7 stays on three to four weeks, sometimes a little longer than
8 that.

9 DR. MCGUIRE: Anatomic sites involved? Is there
10 anything peculiar to certain anatomic sites that would
11 affect the wound healing of partial or full thickness
12 wounds? Yes, Dr. Yurt?

13 DR. YURT: There are a couple of things we have
14 talked about before. Obviously, the thickness of the skin
15 is different in various areas so that the back is much
16 different from the inner part of the upper arm. In
17 addition, depending on what you are studying, if you are
18 studying some type of device or dressing that is put on,
19 certainly putting things over a joint may make a difference.
20 So, if you were going to do comparison studies you would
21 certainly have to do it in a mirror image fashion and not
22 compare a joint with a non-moving surface.

23 DR. GREENHALGH: Another issue is blood supply to
24 the area. That is another important fact. If there is poor

1 blood supply you don't heal as well.

2 DR. MCGUIRE: Other comments on specific sites?

3 Yes, Mr. Richard?

4 MR. RICHARD: Going along that same line, I think
5 it is important also, as was mentioned -- you know, there is
6 a difference between an upper and lower extremity burn too
7 in terms of blood supply and how it is going to heal. So
8 that would have to stay consistent. I don't think you can
9 use various sites and think you are going to come to the
10 same endpoint.

11 DR. MCGUIRE: That is an important point.

12 DR. GREENHALGH: And the other thing depends on
13 the density of the skin. The skin next to a hair follicle,
14 for instead like the scalp, will heal in five days just
15 because there is a higher concentration of skin there. So
16 that is the other thing. So, comparing the scalp to the
17 back would have a marked difference but that is
18 physiologically expected.

19 DR. MCGUIRE: And that follicular epithelium is
20 buried deeper.

21 DR. GREENHALGH: Yes, somewhat but it is more of
22 the concentration. If you take someone who is elderly, that
23 doesn't have much in the way of hair around their legs, for
24 instance, and compare them with a young person who has a lot

1 of hair, the elderly may not heal very well at all. That is
2 one of the risks of doing skin grafts in old people because
3 they don't heal their second degree partial thickness wounds
4 as well.

5 DR. MCGUIRE: Other comments on specific locations
6 of burns? Patient age?

7 DR. GREENHALGH: Well, I just touched on that.
8 The very old and the very young have much more thin skin,
9 which is a problem for taking donor sites, for instance. A
10 partial thickness wound on a young person may be full
11 thickness. On the other hand, if you look at scar a very
12 old person tends to have more loose skin so they don't tend
13 to have as much problem with functional results because
14 their skin can tolerate the shrinkage. If you are doing a
15 chemical peel on someone you are creating an artificial
16 contraction than on people who have looser skin. So, your
17 age does matter as far as certain scarring issues and rate
18 of healing issues.

19 DR. MCGUIRE: Other comments?

20 DR. BERGFELD: Well, there has been all kinds of
21 wonderful work done on older skin and its lack of
22 responsiveness. It is just old and pooped out. It doesn't
23 have any of the necessary nutrients --

24 DR. GREENHALGH: Right.

1 DR. BERGFELD: -- vessels, collagen, blood
2 vessels. It is immunosuppressed. The epidermis is thinner.
3 It doesn't turn over as fast. All that is pretty well known
4 and, obviously, if you had such skin it wouldn't repair as
5 quickly or heal as quickly as someone more youthful who had
6 components in all those parts.

7 DR. SHERIDAN: It is also a big influence on
8 mortality too. Age is the greater predictor of mortality
9 than burn size in our unit. I think that ought to be an
10 exclusion in some of these things.

11 MS. COHEN: I am getting very depressed.

12 [Laughter]

13 DR. MCGUIRE: Ms. Cohen, we are going to have some
14 uplifting message at the end of the day.

15 The burn surgeons use some kind of a nomogram, the
16 name of which I have forgotten. It has age and area, and it
17 is a curve that looks like --

18 DR. SHERIDAN: For?

19 DR. MCGUIRE: Mortality.

20 DR. SHERIDAN: There is an endless list of
21 equations. I think the Zawacky equation was age plus burn
22 size equals percent mortality, and I don't think that is
23 true any more. I think we do better than that. But,
24 certainly, patients who are over 65 do not do as well with

1 their injuries.

2 DR. MCGUIRE: I think we are ready to go to
3 comorbidities, patient condition, concomitant injuries and
4 diseases and wound infection. Would anyone like to comment
5 on comorbid conditions?

6 DR. YURT: Just as we have mentioned before, I
7 think some things we don't want to exclude in these studies
8 because they are going to come up commonly in patients and
9 we want to be able to deal with those, but there are some
10 that are pretty much traditionally considered to be of
11 concern and are left out or used as exclusions, particularly
12 things like steroid use, patients who are immunocompromised
13 prior to their injury. Probably nutritional status should
14 be taken into consideration when you are randomizing
15 patients as well.

16 DR. HUNT: Certainly there are a number of
17 medications, a lot of which we don't know what they do as
18 far as wound and healing. Many of them are on chemotherapy
19 and, obviously, everyone knows that you have to stratify for
20 that and match patients if you can, which is hard to do but
21 it just makes it more complex. That is why we like to do
22 studies in younger patients. Everyone does because there
23 are fewer variables.

24 DR. GREENHALGH: There is a vast literature on

1 factors that impair healing-- you know, diabetes, steroids,
2 chemotherapy agents, renal failure, cancer -- it is out
3 there.

4 DR. BERGFELD: The usual exclusions.

5 DR. HUNT: Most studies exclude diabetics.

6 DR. GREENHALGH: Malnutrition.

7 DR. MCGUIRE: Any other comments on comorbid
8 conditions and their influence on healing?

9 [No response]

10 In clinical trials these covariates can
11 potentially be used as entry criteria, variables for
12 stratification and/or covariates for assessing patient
13 outcome. Please describe the importance of these covariates
14 on safety and efficacy measurements in wound healing studies
15 and how the impact of these covariates might differ for
16 different types of products.

17 We have talked about various entry criteria and
18 variables for stratification. I think some of this has been
19 discussed. Maybe the Agency could tell us what we have left
20 out, if there are some blanks we haven't filled in.

21 DR. WITTEN: I think that you have captured what
22 we wanted on this question pretty well in this discussion.

23 **Topic 8: Follow-up of Study Subjects**

24 DR. MCGUIRE: Let's go to topic 8, follow-up of

1 study subjects: Burn wound products may affect the quality
2 of wound closure. Please discuss how long patients should
3 be followed to assess the durability of wound healing and
4 burn scar cosmesis. Please identify any subgroups of
5 patients that might require shorter- or longer-term follow-
6 up, for instance children.

7 Again, we have discussed that to some degree but I
8 think we could have further discussion if any of the panel
9 members have more to contribute. Yes?

10 DR. GREENHALGH: We did a study at Shriners, in
11 Cincinnati, and we looked at that question of children
12 maturation versus older teenagers, and we found no
13 difference. So, I truly believe that difference in
14 maturation rate in children versus adults really isn't true,
15 unless you compare, like, a 3-year old versus an 18-year
16 old.

17 Now, when you get to a 70-year old person there
18 may be differences, but I am not impressed that there are
19 major differences in the young, that they scar more or
20 whatever if you treat them aggressively like you do adults.
21 There are some issues with compliance and therapy that you
22 have to deal with but I don't believe there is a marked
23 difference.

24 DR. MCGUIRE: Other surgical comments?

1 DR. SHERIDAN: I agree with Dr. Goodwin that
2 lengths of follow-up really need to be meaningful and long
3 to be reasonable, especially in children. I think there are
4 a lot of issues as regards how these wounds will grow with
5 the children and how that impacts on their reconstructive
6 needs.

7 DR. BERGFELD: The discussion stated that one to
8 three years might be appropriate in the short term and then
9 five years would be the chronic look. Are those the
10 guidelines that you are dealing with?

11 DR. SHERIDAN: I take care of a lot of kids and I
12 commonly see their wounds still in a dynamic evolving state
13 two years, three years out. I would certainly be more
14 impressed with a study that showed me a benefit at three
15 years than I would at one.

16 DR. KILPATRICK: May I make an appeal? If the
17 Agency is planning any long-term follow-ups, obviously it is
18 important to minimize loss-to-follow-up because of the
19 difficulties of interpretation of that.

20 DR. MCCAULEY: I think some of us are at
21 institutions where follow-up, especially in children, is
22 pretty high. Certainly, at Shriners Hospital in terms of
23 follow-up I think we capture close to 100% of our patients,
24 certainly five years out from burn injury. But, as Dr.

1 Goodwin has mentioned, at other institutions that may be a
2 significant problem in terms of study design and number of
3 patients who will eventually drop out of the study or not be
4 available for follow-up five years out.

5 DR. GREENHALGH: The other issue about children is
6 that the wounds change but the children change. You know,
7 they have a scar on their arm but their bones get longer.
8 So, that tends to lead to the reason why we follow them
9 long-term because the scar hasn't really changed that much.
10 A lot of it is because they have gotten bigger that these
11 scars now form contractures and you have to deal with them.
12 So, there are a lot of dynamics, not only that the skin is
13 not changing as much or maybe changing differently, but the
14 body is changing a lot too.

15 DR. MCCAULEY: One other point that you just
16 reminded me of is the fact that even reconstruction for
17 release of contractures, or the percentage of patients that
18 require reconstruction for contractures may also be an
19 indicator in some of these studies, especially in children.

20 DR. ROSENBERG: May I ask a question? What we
21 hear about treating scars and, to a degree, keloids, has
22 changed a lot in the last couple of years with the use of
23 the occlusive sheeting. Has that made any impact on your
24 practice, the silicone type of materials?

1 DR. HUNT: I daresay that there are not a lot of
2 large prospective, well-controlled, randomized, blinded
3 studies. So, I think that is another one of the sort of
4 anecdotal, things in burns; I don't know about dermatology.
5 A big problem with that, among other things, is compliance
6 of the individual. But I think that is an unsolved,
7 unresolved answer in burns, just how good silicone is.

8 We just had something a few years ago thrown back
9 into the burn world that I never expected. There is one
10 investigator -- granted, it may be small, but he questioned
11 if pressure garments are appropriate. Has anyone ever done
12 a prospective, controlled, randomized study on pressure
13 garments? And the answer is no. So, I mean, we are almost
14 going back to ground zero. You know, intuitively we know
15 they work, but scientifically do we? I would like to hear
16 what other people think about silicone. You seem to have a
17 disturbed look on your face.

18 DR. ROSENBERG: No, I appreciate your frankness.

19 DR. GREENHALGH: I can agree with that. I am not
20 convinced that silicone itself works better, but I don't
21 think our treatment for hypertrophic scars has really
22 changed that much. There have been things out there.
23 Interferons are being looked at. But we still go back to
24 the basics, massage, pressure, stretching therapy.

1 DR. ROSENBERG: Are you using the silicone
2 preemptively?

3 DR. GREENHALGH: We have tried it here and there.
4 The answer is not out there yet.

5 DR. SHERIDAN: I will speak for our unit and maybe
6 take a slightly contrary point of view. It is in the tool
7 box that you have when dealing with these scars, and I think
8 that the most important tool is probably the treatment of
9 the wound acutely so you don't have this problem to deal
10 with so much. We have used for broad areas of hypertrophic
11 scarring pressure garments, believing that they would help,
12 particularly in smaller children if they are properly fit.
13 We have also used silicone sheeting and steroid injections
14 in small areas of very important, highly charged cosmetic
15 areas. It is my opinion that there are a substantial number
16 of children that do benefit from that. But, as Dr. Hunt
17 says, the data upon which you hang that hat is very weak,
18 but it is a personal opinion that there are scars that do
19 respond to that.

20 DR. YURT: We use silicone and have been happy
21 with it. The problem, as has been mentioned before, is that
22 we don't have many things to use and so we will frequently
23 end up putting some of these things on patients that we have
24 not had much success with and we are just trying, sort of

1 groping for straws. But I think it is important, if studies
2 are going to be done, to recognize particularly the
3 hypertrophic scar and the pressure question. I suppose you
4 can deal with that by randomizing and making sure that both
5 areas are treated the same way. But I also am somewhat
6 concerned that we have no scientific data that supports the
7 use of that.

8 DR. MCGUIRE: Would any of the dermatologists like
9 to comment on use of silicone sheeting?

10 DR. HUNT: Do you use it or not? I would be
11 curious. You all see a lot of scars. What do you use?
12 What do you recommend?

13 DR. BERGFELD: We use interlesional
14 corticosteroids I think more uniformly than anything else.
15 But the silicone has come into our practices. We have the
16 same issues that you have as to its effectiveness, and only
17 one-person, small collective studies have been done.

18 DR. ROSENBERG: Our practice is keloids. So it is
19 marketed for keloids. Do burns keloid?

20 MR. RICHARD: I think that is a very good
21 question, and I think that would be something for either
22 inclusion or exclusion criteria in any study that is being
23 done, to come up with a way to define -- and I don't know
24 what that definition is -- the difference between a

1 hypertrophic scar and a keloid scar. Clinically there is
2 certainly a difference in terms of the keloids being lobular
3 and extending beyond the boundaries of the wounds, and that
4 sort of thing, as opposed to the hypertrophic scar. But
5 oftentimes you see the insert materials -- that is what we
6 are talking about, the silicone, the medical grade mineral
7 oil, the hydrogels; we are talking about insert material,
8 you know, making claims of taking care of keloid scars and I
9 am not so certain that they are keloid to begin with.

10 DR. BERGFELD: Histologically you can tell the
11 difference, but there is a mixed group that have components
12 of both.

13 DR. MCCAULEY: I think keloids in burns, they do
14 occur but I don't think they occur that frequently. What we
15 do see are patients that have tremendous hypertrophic scars
16 that sometimes get classified as keloid but if you go back
17 and look at the original pictures, they are all within the
18 area of the burn injury. Even though they have a tremendous
19 proliferative response in collagen accumulation, I still
20 think they are hypertrophic scars.

21 DR. MCGUIRE: So what we have said is that
22 silicone sheeting is used. We hope it is working; we are
23 not sure if it is working, and it probably needs to be
24 looked at.

1 DR. GREENHALGH: I have one other comment,
2 especially with the interest in dermatitis. I have seen a
3 lot of dermatitis with the silicones just because of the
4 moisture, or whatever, but that has been a problem I have
5 had, a lot of it because of that.

6 **Topic 9: Product Indications**

7 DR. MCGUIRE: We are ready for topic 9, I think.
8 What are the characteristics of thermal burns, chemical
9 burns, electrical burns and epidermal disorders requiring
10 skin replacement? At this point you have to believe that
11 the Agency just looked up everything they hadn't already
12 covered in the preceding three pages. We have thermal
13 burns, chemical burns, electrical burns, epidermal disorders
14 requiring skin replacement, such as epidermolysis bullosa --
15 they put that in for me -- congenital nevi that would
16 require separate studies to demonstrate product
17 effectiveness. In this discussion please consider the
18 following types of products. Again, these are items that we
19 have discussed in a different context with thermal burns,
20 earlier this morning and afternoon: antimicrobial agents,
21 debriding agents, skin substitutes, growth factors and other
22 products.

23 DR. SIMMONS-O'BRIEN: I have a question. I would
24 love to know how the surgeons handle severe PUVA burns,

1 which are different. They area phototoxic injuries based on
2 PUVA psoralen plus ultraviolet A light. We have seen some
3 incredible burns. People can die from PUVA burns because
4 UVA peaks at 48 hours, and depending on how mush psoralen
5 someone has taken. Given that classically they do not scar,
6 these burn injuries, but given that they can be life-
7 threatening, have any of our panel ever encountered PUVA
8 injuries and how do you handle them?

9 DR. MCGUIRE: Would you define for those who don't
10 know --

11 DR. SIMMONS-O'BRIEN: I am sorry. PUVA is an
12 acronym, P-U-V-A. That stands for psoralen, which is
13 foumarin cumarin compound that is activated by light that we
14 use in conjunction with wave lengths of light, UVA but
15 sometimes UVA and UVB, to treat patients who have most
16 commonly psoriasis that is extensive an severe eczematous
17 dermatoses. Those are the most common. We use it for many,
18 many, many other things as well. I think it is a problem
19 for us in institutions that use a lot of phototherapy --
20 that is what this technique is called, and it is fraught
21 with havoc because you don't follow your patients out of the
22 door and, depending on how much sunlight they get that day,
23 if it is a warm day, a summer day and they are not covered
24 or they forget to tell you they are going to Florida for the

1 weekend -- you know, things like that, along with the
2 potential of burning that patient in the box for various
3 reasons, and if it also happened they didn't tell you that
4 they just started taking hydrochlorothiazide, what-have-you,
5 but there are a lot of reactors so that you can end up
6 getting severe problems with that. I just wanted to know
7 about any experience that panel members may have had.

8 DR. SHERIDAN: We don't see a lot. We see one or
9 two of these a year, which come in as TENS patients. They
10 are usually elderly. Perhaps they are just more susceptible
11 with their thinner skin. We have had good luck treating
12 them just like TENS patients.

13 DR. BERGFELD: The PUVA in my mind is both a
14 chemical as well as a light burn. So, it is a thermal burn.
15 But I wonder if the surgeons can tell us if there is truly a
16 difference between a thermal and chemical wound, or
17 electrical, or is it truly just the nature of the damage
18 done to the skin? I mean, is that what you deal with in the
19 end, what happens after such a burn, or is there a specific
20 difference in the burn itself?

21 DR. GREENHALGH: I think it depends on what the
22 agent is doing. If you want an agent, for instance in TENS,
23 that you want to optimize biologic environment, indeed, what
24 you are concerned about is creating a biologic surface, such

1 as pig skin, or allograft, or Biobrane that optimizes
2 healing, and that product is designed to optimize
3 epithelialization, which is the same process that you have
4 for partial thickness burns.

5 In a chemical burn the damage is done differently
6 but we will still end up grafting them, and have the same
7 principles for graft take or preventing invasion by
8 bacteria. The same principles usually apply to a lot of
9 these same things. Like the PUVA, yes, it is caused a
10 different way but what are you trying to do? You are trying
11 to optimize epithelialization and prevent further damage.
12 So the physiologic principles are basically the same. If
13 you have a product that optimizes epithelialization or that
14 prevents overgrowth of infection and allows for optimal
15 healing, I don't think the FDA should look at it as being a
16 different wound and you need a different study for it. It
17 is the same physiologic process for healing, I think.

18 DR. BERGFELD: Is there any residual of the
19 chemical though that offers a hazard over time greater than
20 the electrical or greater than the thermal? The residual
21 chemical?

22 DR. GREENHALGH: I would say most of the time not.
23 Electrical is a different story in that damage is done to
24 the microvasculature and there is ongoing, continuing damage

1 to tissues. A lot of times a muscle looked at one day, the
2 next day is dead and it keeps on progressing. The
3 pathophysiology is a little bit different there, but then
4 those patients with electrical burns that need grafting, the
5 same principles apply. A lot of the thermal parts of that
6 are treated a different way when you deal with a muscle and
7 other injury areas.

8 DR. MCGUIRE: Dr. Sheridan, do you have a comment?

9 DR. SHERIDAN: The only comment I have is that at
10 least in our unit it is often much more difficult to read
11 the depth of chemical burns initially because, as David
12 said, the physiology of the injury is different, and it is
13 quite common to under-call the depth. So, that would have
14 to be at least acknowledged in the protocol design. Also,
15 the electrical burns tend to be very deep and so the
16 penetration of the agent is a bigger issue.

17 DR. YURT: I think from the standpoint of chemical
18 burns, I personally would be much less likely to occlude
19 that wound immediately even though we copiously irrigate it,
20 and so forth. Because of the lack of knowledge of the depth
21 of the injury and the possibility of the chemical still
22 being there, I would be somewhat hesitant to occlude that,
23 whereas I may well do that in a partial thickness thermal
24 injury. I guess the one chemical that I would be concerned

1 about and would probably stay away from in any studies would
2 be hydrochloric acid because of the intense tissue damage
3 that can occur and the mortality that can occur associated
4 with that compared to the other chemicals.

5 DR. GREENHALGH: I agree that the pathophysiology
6 of the damage is different, but whether a product should be
7 approved for a chemical burn and not for a thermal burn, or
8 vice versa, I don't think is the issue. We still use these
9 agents to help heal the wounds, and I think it shouldn't be
10 excluded in a trial design.

11 I agree that you probably wouldn't want to have an
12 electrical burn compared with a thermal burn because there
13 are so many other things that confuse the data, but as far
14 as whether you can apply the same principles for a thermal
15 burn to a chemical burn, I think basically you can.

16 DR. BERGFELD: Well, it sounds to me like you walk
17 into the evaluation by realizing what you have day one,
18 reassessing it on day two, and there may be a difference.
19 You may have to wait a week or so --

20 DR. GREENHALGH: Absolutely.

21 DR. BERGFELD: -- until everything evens out, no
22 matter what the cause of the burn, so that you know what
23 surgical procedures need to be done and what bioactive
24 agents need to be applied.

1 DR. GREENHALGH: Right. For example, if you have
2 a necrotizing fasciitis, I mean, when you are treating these
3 injuries you have to stop the damaging process, and it may
4 take a week or two to stop the damaging bacteria in that
5 case, but then it still comes down to having to cover the
6 wound with something, and when you are covering the wound
7 the same wound coverage principles apply.

8 DR. BERGFELD: Then you go back to the original
9 sheet that says you need to get rid of the devitalized
10 tissue and all the component parts and then proceed.

11 DR. GREENHALGH: Right.

12 DR. MCGUIRE: There is a provocative item here,
13 skin substitutes. What is looking good in the surgical
14 field? I guess we could start by saying there is really no
15 substitute for skin. That is the gold standard --

16 [Laughter]

17 -- and so far we don't have a good substitute. So
18 we are looking for some kind of "wanna be" skin that is
19 going to be retained, provide a barrier, prevent infection
20 and, ideally, be very durable.

21 DR. GREENHALGH: My philosophy is that some day we
22 are going to have a good one, and we are still in the early
23 phase, a model T-Ford stage as far as skin substitutes go.
24 I think we need to keep working on them, and there are

1 things out there that have their purposes for specific
2 indications but none of them are at the stage that you can
3 put a nice -- I mean, if you have a small burn that needs a
4 graft, the autograft is still going to be much better than a
5 skin substitute at this point.

6 DR. SHERIDAN: So, the question is about how skin
7 substitutes relate to these non-thermal diagnoses?

8 DR. MCGUIRE: I think we could expand it to
9 thermal or non-thermal. If we are going to talk about skin
10 substitutes we can just open up the question and talk about
11 any kind of injury.

12 DR. GOODWIN: I think at least for some of these
13 epidermal disorders Gretchen's organization has used
14 xenograft for patients with toxic epidermal necrolysis
15 which, if nothing else, makes the patients much more
16 comfortable and they seem to heal quite well. They re-
17 epithelialize under the porcine xenograft. I think there
18 are other centers that have used Biobrane and other totally
19 synthetic products to treat these epidermal sloughing type
20 diseases.

21 DR. MCGUIRE: The toxic epidermal necrolysis is a
22 wonderful disease to treat that way because, since the
23 injury is so superficial, you get re-epithelialization
24 through the hair follicles, and you can watch those cells

1 come up and invest the xenograft or the allograft, and they
2 just chuck it as they come up and join. So, that is a
3 marvelous example in which the skin substitute is very
4 effective.

5 I think for disorders that are not self-healing,
6 like toxic epidermal necrolysis, we need a different
7 product. The Agency put epidermolysis bullosa here, I think
8 maybe to see if I was reading my background material. I
9 did. We have a different problem there. Most of you think
10 of EB as being a blistering disease, which it is, but the
11 blisters very quickly turn into chronic erosions and chronic
12 erosions don't heal for months, years, more years. Then
13 these children and young adults die of squamous carcinoma,
14 which is biologically a very aggressive squamous carcinoma,
15 much different from the light-induced squamous carcinoma
16 that dermatologists are used to dealing with. This is much
17 more like a nasopharyngeal carcinoma.

18 In this population of young adults we need to
19 replace skin, and we don't have a very good source of skin
20 because most of these children and young adults don't have a
21 lot of skin to work with. So, we need a solution there.

22 It is hard to believe but we can take split
23 thickness skin grafts from these children and even full
24 thickness skin grafts from an inguinal full thickness donor

1 site and cover some of the areas. But the carcinomas in
2 these children and young adults can be quite large. I mean
3 the area can be the size of your hand. So, there is a
4 specific need here.

5 DR. SHERIDAN: I guess I am a little confused. We
6 could all talk for hours about the state-of-the-art of skin
7 substitution and where it is going. I just need a little
8 structure to specifics.

9 DR. MCGUIRE: Well, what would the Agency like to
10 know about specifically?

11 DR. WITTEN: I think what we are looking for is
12 discussion, and you have already discussed a good deal to
13 what extent in a study of one of these types of injuries you
14 can apply the information from that study to assume the
15 product will work in another setting. We were giving you
16 here some examples of products, and we were wondering
17 whether a study that demonstrated effectiveness of one of
18 these products in one clinical setting could be expected to
19 be equally effective in another setting. So, I think at
20 what point you would consider that you would be able to do
21 that you have already discussed somewhat. It would be
22 helpful if you had any additional comments on that,
23 especially as it relates to these other disorders or these
24 other products that are listed here.

1 DR. SHERIDAN: I think it is a great point that
2 TENS and superficial second degree burn donor sites are all
3 reasonably homogeneous physiologically in terms of their
4 treatment with temporary skin substitutes of any number of
5 types, with the endpoints being epithelialization, pain
6 control etc. I think they could be homogenized.

7 DR. YURT: I suppose, as Rob just pointed out, the
8 bottom line is maybe depth of injury when you are talking
9 about these things. I think there has been some confusion
10 with some products being used, advocated to be used, say, on
11 both partial and full thickness burns. But as things are
12 starting to fall out, I think we really have to consider the
13 depth and probably different uses, depending on the depth of
14 the injury that you are talking about. So, to look at these
15 various types of injury I think depth would be one of the
16 bottom lines. If it is at the same depth, then it probably
17 should be able to be transferrable from one to the other.

18 DR. GOODWIN: But there is a caveat. The few
19 patients when I was working with Dr. Yurt that we got
20 involved with, with bad EB, even grafting them with their
21 own skin didn't seem to work at all. I mean it is a
22 dreadful, recalcitrant problem. So, I don't know that any
23 of these would be transferrable to a disease like that.

24 DR. BERGFELD: I would like to make a comment

1 about that too. I think that on a temporary basis some of
2 the products that might be developed for the burns we have
3 been discussing might be helpful, but basically biologically
4 these skins are different and default. They have major
5 differences in development. As you know, they never do
6 produce normal skin. So, I am not so sure that anything you
7 would do would be to produce normal skin. Your endpoint
8 would be coverage, pain reduction and infection reduction
9 and, hopefully, a little longer a graft that held for
10 periods of time so that there wouldn't be an immediate
11 recurrence, and with any damage to these skins, these skins
12 break down. They break down anyway in the EB. The toxic
13 epidermal necrolysis is different but is still a major
14 problem.

15 DR. MCGUIRE: I don't want to turn this into an EB
16 symposium, and I won't. I would like to make one point,
17 that is, areas of skin that have been injured and have
18 blistered are much more likely to blister and be injured
19 again, and you can graft uninvolved skin in EB to areas of
20 involvement and have an outcome that is not bad, especially
21 in terms of covering tumor site.

22 I would like to hear from the Agency. I would
23 like to know if there are any areas that I have slid by
24 inadvertently.

1 DR. WITTEN: I would like to thank everyone here
2 for participating. I think from our point of view this has
3 been a very helpful discussion, and we will be moving
4 forward, hopefully, to include this information in a draft
5 of a guidance document.

6 DR. MCGUIRE: I can tell by the sound of the books
7 and paper rustling that we are about to leave. I would
8 particularly like to thank the outside experts who came and
9 set an example for a cooperative discussion between surgeons
10 and dermatologists. It is probably the first time in fifty
11 years that has happened. We ought to do it again sometime.
12 Thank you very much.

13 [Whereupon, at 2:40 p.m. the proceedings were
14 recessed.]

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