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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE
OPEN SESSION

Thursday, July 29, 1999

8:48 a.m.

Conference Rooms G and H
Parklawn Building
5600 Fishers Lane
Rockville, Maryland

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Mary Cornelius, Executive Secretary

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Jenelle E. Foote, M.D.
Robert H. Hawes, M.D.
Joseph H. Steinbach, Ph.D.
Leonard L. Vertuno, M.D.

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Michael P. Diamond, M.D.
Patrick T. Hunter, II, M.D.
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P R O C E E D I N G S

1
2 DR. A. KALLOO: Just to let you know we are
3 waiting on some of the panel members to get here. We still
4 don't quite have a quorum to proceed. So, as soon as they
5 arrive, we will begin the meeting.

6 [Pause.]

7 DR. A. KALLOO: May I have your attention, please.
8 Either because of weather or transportation difficulties, we
9 are still waiting on one or two members to arrive. So, the
10 plan is to reconvene at 9:15.

11 [Recess.]

12 DR. A. KALLOO: Good morning again. I think we
13 will proceed with this morning's session.

14 I would like to call to order this meeting of the
15 Gastroenterology and Urology Devices Panel. I would to note
16 for the record that the voting members present constitute a
17 quorum as required by 21 C.F.R. Part 14.

18 **Introductions**

19 Would each member introduce himself or herself,
20 designate specialty, position title and institution and
21 status on the panel, voting member or consultant, starting
22 on my immediate right.

23 MS. CORNELIUS: I am Mary Cornelius and I am the
24 Executive Secretary of this panel.

25 DR. DONATUCCI: Craig Donatucci. I am Associate

1 Professor of Urology at Duke University.

2 DR. N. KALLOO: Naida Kalloo. I am Assistant
3 Professor in Urology at National Naval Medical Center at
4 Bethesda. I am a pediatric neurologist there.

5 MR. SEGERSON: I am Dave Segerson, Associate
6 Division Director, Reproductive, Abdominal, Ear, Nose, and
7 Throat Radiological Devices. I am the FDA representative at
8 this meeting.

9 DR. BENNETT: I am Alan Bennett. I am a medical
10 consultant and Professor of Urology at Montefiore and Albert
11 Einstein College of Medicine.

12 DR. VERTUNO: Leonard Vertuno. I am a
13 nephrologist and Associate Dean at Loyola University School
14 of Medicine, Maywood, Illinois, and I am a voting member.

15 MS. NEWMAN: I am Diane Newman. I am a nurse
16 practitioner in practice in Philadelphia in incontinence,
17 and I am the consumer representative. I am a non-voting
18 member.

19 DR. DIAMOND: My name is Michael Diamond. I am
20 Professor of Obstetrics and Gynecology at Wayne State
21 University in Detroit, Michigan, and I am a temporary voting
22 member.

23 DR. A. KALLOO: My name is Anthony Kalloo. I am
24 Associate Professor of Medicine at Johns Hopkins University
25 and the Clinical Director of Gastroenterology, and I am a

1 voting member.

2 I will now turn the meeting over to Mary, who will
3 read the Executive Secretary statement.

4 **Executive Secretary's Statement**

5 MS. CORNELIUS: Good morning. Before we begin, I
6 would like to read a statement concerning appointments to
7 temporary voting status.

8 Pursuant to the authority granted under the
9 Medical Devices Advisory Committee Charter, dated October
10 27, 1990, as amended April 20, 1995, Dr. Richard E.
11 Deitrick, Michael P. Diamond, Patrick T. Hunter, and Naida
12 B. Kallou have been appointed as voting members by Dr. David
13 W. Feigal, Director of the Center for Devices and
14 Radiological Health, for this meeting of the
15 Gastroenterology and Urology Devices Panel.

16 As you are aware, we have some members coming that
17 have not arrived yet, and we can only surmise there may be
18 some problems at the airport. Dr. Foote, thank you. You
19 are not the only one who had trouble getting here.

20 To determine if any conflict existed, the agency
21 reviewed the submitted agenda and all financial interests
22 reported by the committee participants. The Conflict of
23 Interest Statutes prohibits special government employees
24 from participating in matters that could affect their or
25 their employers' financial interests. However, the agency

1 has determined that the participation of certain members and
2 consultants, the need for whose services outweighs the
3 potential conflict of interest involved, is in the best
4 interest of the government.

5 A waiver is on file for Dr. Leonard Vertuno and
6 waivers have also been granted to Ms. Diane Newman, Drs.
7 Michael Diamond, Craig Donatucci, and Patrick Hunter for
8 their interest in the firms that could potentially be
9 affected by the panel's deliberations. The waivers allow
10 these individuals to participate fully in today's
11 deliberations.

12 A limited waiver has been granted to Dr. Jenelle
13 Foote that allows her to participate in the discussion, but
14 not vote on the PMA before the panel today.

15 A copy of these waivers may be obtained from the
16 agency's Freedom of Information Office, Room 12A-25 of the
17 Parklawn Building.

18 We would also like to note for the record that the
19 agency took into consideration certain matters regarding Ms.
20 Newman and Drs. Diamond, Donatucci, Foote, and Hunter.
21 These panelists reported current and past interest in firms
22 at issue, but not in matters related to what is being
23 discussed today. Since these matters are not related to
24 specific issues of this meeting, the agency has determined
25 that they may participate fully in today's deliberations.

1 In the event that the discussions involve other
2 products or firms not already on the agenda for which the
3 FDA participant has a financial interest, the participants
4 should excuse him or herself from such involvement and the
5 exclusion will be noted for the record.

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

11 Dr. Kalloo will ask all persons making statements
12 either during the open public meeting or during the open
13 committee discussion portions of the meeting to state their
14 name, professional affiliation, and disclose whether they
15 have any financial interest in any medical device company.

16 Finally, I would like to remind you that the
17 remaining panel meeting scheduled for 1999 is November 18th
18 and 19th. This meeting is only tentative. The tentative
19 panel meetings for 2000 are January 27 and 28, April 13 and
20 14, August 31 and September 1, and November 30 and December
21 1. If the panel meeting is going to be held, I will notify
22 panel members at least two months in advance of the meeting.

23 I will turn the microphone back to Dr. Kalloo.

24 DR. A. KALLOO: Thank you, Mary.

25 I would like to ask Dr. Foote to just introduce

1 herself, her specialty.

2 DR. FOOTE: My name is Dr. Jenelle Foote. I am in
3 private practice in Atlanta with clinical affiliations with
4 Emory University and Morehouse School of Medicine. My
5 specialty is that of general urology with subspecialty
6 training and expertise in neurourology and female voiding
7 dysfunction.

8 DR. A. KALLOO: Thank you.

9 **Open Public Hearing**

10 We will now proceed with the Open Public Hearing
11 section of this meeting.

12 I would ask at this time that all persons
13 addressing the panel come forward to the microphone and
14 speak clearly, as the transcriptionist is dependent on this
15 means of providing an accurate transcription of the
16 proceedings of the meeting.

17 Dr. Hawes, welcome, glad to see you. If you could
18 just introduce yourself and your title and specialty.

19 DR. HAWES: My name is Rob Hawes. I am a
20 Professor of Medicine at the Medical University of South
21 Carolina. I am a gastroenterologist.

22 DR. A. KALLOO: And your voting status?

23 DR. HAWES: I am a voting member.

24 DR. A. KALLOO: Before making your presentation to
25 the panel, please state your name and affiliation, and the

1 nature of your financial interests in that company. Let me
2 remind you that the definition of financial interests in the
3 sponsor company may include: compensation for time and
4 services of clinical investigators, their assistants and
5 staff, in conducting the study, and in appearing at the
6 panel meeting on behalf of the applicant; direct stake in
7 the product under review, that is, inventor of the product,
8 patent holder, owner of shares of stock, et cetera; owner or
9 part owner of the company.

10 Of course, no statement is necessary from
11 employees of that company.

12 I would ask that all persons addressing the panel
13 come forward to the microphone and speak clearly as the
14 transcriptionist is dependent on this means of providing an
15 accurate transcription of the proceedings of this meeting.

16 Before making your presentation to the panel,
17 state your name and affiliation, and the nature of any
18 financial interest you may have in the topic you are going
19 to present.

20 The first speaker as listed on the agenda is Dr.
21 Roger Dmochowski from the AUA, American Urologic
22 Association.

23 **Roger R. Dmochowski, M.D.**

24 DR. DMOCHOWSKI: Good morning. My name is Roger
25 Dmochowski. I am a practicing urologist in Dallas, Texas.

1 I am here to represent the opinions of the American Urologic
2 Association in this research. I have a clinical appointment
3 both at the Uniformed Services University and also at the
4 University of Texas Southwestern. I have no financial
5 affiliations with either of the companies bringing forth
6 their products today.

7 I would like to make just some general supporting
8 statements from the American Urologic Association regarding
9 ongoing industry-sponsored research in incontinence.

10 The Executive Committee of the Board of Governors
11 of the American Urologic Association, as well as those with
12 specific interests in neurourology and female neurology,
13 such as Dr. Foote and myself, feel strongly that industry-
14 supported research is crucial for the development of new and
15 novel techniques for the delivery of incontinence treatment
16 for patients other than surgical techniques.

17 It has become obvious from our improved
18 understanding of the pathophysiology of stress urinary
19 incontinence in both females and males that surgery is not
20 the only nor the best option for a significant percentage of
21 patients. We better understand the intrinsic urethral
22 mechanism, and there are now several methods by which we can
23 deal with the intrinsic urethral mechanism other than pure
24 surgical techniques.

25 Basically, those method involve two essential

1 types of therapeutic delivery. One is the utilization of
2 various injectable or bulking agents of which there are
3 basically three categories. The three categories are
4 biologics, either autologous or non-autologous, and
5 synthetic materials.

6 The other broad option for treatment of the
7 intrinsic urethral mechanism other than surgery is the
8 utilization of various device-based technologies, such as
9 intraurethral mechanisms, mechanical mechanisms, and/or
10 injectable delivery mechanisms.

11 It is the opinion of the AUA that development of
12 these mechanisms and also the injectables represents the
13 next significant frontier in development in the treatment of
14 stress urinary incontinence other than surgical techniques
15 which continue to evolve.

16 We are very much in favor of the development of
17 these techniques. Specifically, in the injectable market,
18 the development of the biologics really holds great promise.
19 We have a gold standard, which is bovine collagen, which is
20 limited both due to durability and allergic phenomena.

21 We are continually seeking new and better options
22 with more longevity and durability in terms of response and
23 also less antigenicity and allergic reactions.

24 In terms of mechanism technologies that we are
25 looking for, we are looking for small mechanical devices

1 that can be utilized by patients without significant
2 discomfort, with relatively broad spectrums of time delivery
3 in terms of not having to be removed every one to two weeks,
4 but rather can dwell for anywhere from 30 to 90 days with
5 relative stability of response and stability of mechanical
6 support to the patient.

7 So, from the standpoint of the American Urologic
8 Association, both the injectable and device-driven
9 technology represents a frontier for the future in the
10 treatment of the intrinsic urethral mechanism, and we
11 support it in its entirety from the general standpoint.

12 Thank you very much.

13 DR. A. KALLOO: Thank you.

14 Dr. Hunter just arrived, so while he settles down,
15 I want to just ask him to introduce himself, his title,
16 specialty, and his voting status. Sorry to pull you to the
17 table so quickly, Dr. Hunter.

18 DR. HUNTER: Pat Hunter, Clinical Assistant
19 Professor, University of Florida. I am also in private
20 practice in Orlando. I have no affiliation with any of the
21 companies or products being discussed, no financial
22 interest. I am a voting member.

23 DR. A. KALLOO: Thank you.

24 Next, Dr. Thomas Gross will give a presentation on
25 Postmarket Evaluation at the FDA's Center for Devices and

1 Radiological Health.

2 **Dr. Thomas P. Gross**

3 DR. GROSS: Good morning. My name is Tom Gross.

4 I am the Director of the Division of Postmarket Surveillance
5 at CDRH. This morning I would like to take a few minutes of
6 your time to talk about postmarket evaluation at CDRH.

7 We, in the Office of Surveillance and Biometrics,
8 think that it is important that advisory panels are aware of
9 postmarket programs and activities because they may directly
10 relate to your deliberations about a product's safety and
11 effectiveness.

12 [Slide.]

13 The objectives of this presentation are threefold:
14 one, to describe a few of the key methods of device
15 postmarket evaluation; present challenges in better
16 accomplishing postmarket evaluation; and describe the
17 pivotal role that the advisory panels can play in this
18 arena.

19 [Slide.]

20 This slide, entitled "From Design to
21 Obsolescence," makes three key points. One, it depicts the
22 natural history of medical devices from design to lab/bench
23 testing, clinical testing, FDA review, and importantly,
24 postmarket evaluation.

25 Secondly, it depicts the continual feedback loops

1 throughout the process leading to product improvements.
2 Postmarket evaluation has an important part to play in that
3 process, and the rest of this talk will focus on three
4 programs within postmarket evaluation - the MDR program,
5 postmarket surveillance under 522, and post-approval under
6 PMA.

7 Thirdly, the clinical community including the
8 advisory panel has a crucial role to play in this process of
9 continual product improvement.

10 [Slide.]

11 As products move into the marketplace, questions
12 of potential public health interests may arise. There may
13 be questions about a product's long-term safety, about the
14 performance of the device in community practice particularly
15 as it moves outside the confines of clinical trials.

16 There may be concerns about effects of change in
17 user setting, going from professional to home use, for
18 instance, or concerns about effects of incremental changes
19 in technology.

20 There may be concerns also about adverse events or
21 unusual patterns of adverse events.

22 [Slide.]

23 Now, let's focus on some of the programs that may
24 address some of these questions starting with the Medical
25 Device Reporting program or MDR.

1 MDR is a national surveillance system of voluntary
2 and mandatory reports. The mandatory portion started in
3 1984 under the Medical Device Amendments, requiring
4 manufacturers to report deaths and serious injuries if a
5 medical device may have caused or contributed to the event.
6 They were also required to report malfunctions.

7 Beginning in 1990, under SMDA, all user
8 facilities, particularly nursing homes and hospitals, had to
9 report deaths to the FDA and serious injuries to the
10 manufacturers.

11 [Slide.]

12 All told, in the history of the MDR program, we
13 have received slightly more than 1 million reports in our
14 database. However, it was only in the early 1990s that we
15 started receiving huge numbers of reports, and currently we
16 receive about 100,000 reports per year.

17 These are submitted on standardized forms which
18 capture several data elements including device specifics,
19 event description, pertinent dates, and patient
20 characteristics.

21 Reports unfortunately often have very limited
22 information, even information on age and gender is missing
23 from many, many reports, but they also provide critical
24 signals to the FDA, signals that we take action on.

25 [Slide.]

1 Now, what are some of the actions prompted by the
2 MDR program? Upon further investigation of these adverse
3 event reports, we may be doing directed inspections of
4 manufacturers or user facilities. It may ultimately lead to
5 product injunctions or seizures, product recall, namely, an
6 example of a recent recall involving blood tubing associated
7 with leaking of infected blood into dialysis machines.

8 We have had several patient and physician
9 notifications over the past few years, again, many related
10 to dialysis machines and, in particular, dialyzer membranes.
11 Actions may also lead to additional postmarket study.

12 [Slide.]

13 We at CDRH have two authorities by which we can
14 conduct postmarket studies. One is a statutory authority
15 under FDAMA, Section 522, entitled "Postmarket
16 Surveillance." Another is our post-approval authority under
17 PMA regulation.

18 Section 522 was originally mandated in SMDA 1990,
19 and was changed significantly in FDAMA 1997. The 1990
20 version had categories and lists of devices, the
21 manufacturers of which were required to do postmarket
22 studies on regardless of whether there were any pertinent
23 public health questions.

24 Those categories and lists were deleted and they
25 are no longer part of the FDAMA 1997 version. However, the

1 '97 version retained FDA's discretionary authority to order
2 postmarket surveillance on products for which we had public
3 health concerns.

4 Now, post-approval refers to PMA products and it
5 is reserved strictly for PMA products and the studies
6 conducted under post-approval are referred to as conditions
7 of approval studies. Section 522 extends our authority to
8 cover Class II and III 510(k) products whose failure may
9 present a public health problem.

10 Now, both authorities are seen as a complement to
11 the premarket efforts to continually assure product safety
12 and effectiveness in the marketplace.

13 [Slide.]

14 Now, in implementing the FDAMA version of Section
15 522, we developed criteria to help guide our deliberations
16 about when to impose postmarket surveillance on Class II and
17 III products. The principal criterion is that there has to
18 be a critical public health question.

19 This can result from a "for cause" issue, such as
20 a notable adverse event or patterns of adverse event. It
21 may be linked to concerns about new or expanded conditions
22 of use, or concerns about safety related to the evolution of
23 the technology.

24 The second criterion has to do with consideration
25 of other postmarket strategies, 522 may not be the

1 appropriate strategy to answer the public health question of
2 interest - perhaps an inspection, perhaps some aspect of the
3 quality systems regulation would better handle the issue.

4 Thirdly, the studies have to be practical and
5 feasible to conduct. For instance, for long-term studies we
6 need to be somewhat assured that sufficient patient follow
7 up is there.

8 A related question - how will the data be used?
9 This is especially important for rapidly evolving
10 technology. By the time the studies are done, the data may
11 be obsolete.

12 Lastly, it has to be of a high priority for the
13 center, for yourselves, and for the manufacturing community.

14 [Slide.]

15 Once we decide to impose postmarket surveillance
16 under 522, there are several approaches we may use. We
17 should attempt to choose the appropriate study design to
18 match the public health question of interest and to choose
19 the least burdensome approach.

20 Now, that may mean something as least burdensome
21 as a detailed review of the complaint history and
22 literature, non-clinical testing of a device, use of
23 existing databases, or telephone or mail follow up of
24 patients. It may require something more sophisticated, such
25 as use of product registries, case control studies, and

1 rarely, we might turn to randomized trials.

2 [Slide.]

3 Now, what are some of the frustrations we have
4 experienced in conducting postmarket surveillance in the
5 postmarket period?

6 I have mentioned before that the rapid evolution
7 of technology may make studies obsolete. We should
8 anticipate that. There are lack of incentives for industry
9 to conduct these studies. Industry may view these studies
10 as being the bearers of only bad news for their products.
11 We need to change the paradigm and make it useful for
12 industry to conduct these studies.

13 There may be lack of interest in the clinical
14 community. Clinicians may be much more interested in
15 studying cutting-edge technology as opposed to issues
16 related to mature technologies.

17 As in the case of SMDA 1990, there may be lack of
18 clearly specified public health questions.

19 [Slide.]

20 Now, what is the challenge to the advisory panel
21 and really the challenge to us all?

22 When considering postmarket studies, whether they
23 are post-approval or 522, we need to ensure that these are
24 of primary importance, that they are just not nice to know,
25 that they are central to the issue of the safety and

1 effectiveness of the product, that they justify the
2 resources, that they are practical and feasible.

3 We need to clearly specify the public health
4 question, and we need to note the clinical and regulatory
5 relevance of answering the question - what will do with the
6 data? Are the data there to assure us that what we see in
7 the postmarket arena is what we have seen premarket, are
8 they there to address residual concerns about the product,
9 are they there to capture untoward events?

10 [Slide.]

11 Lastly, this is my last slide, just a look into
12 the future of MDR and postmarket surveillance.

13 For medical device reporting, we are moving more
14 and more away in terms of efficiency from individual
15 reporting to summary reporting of well known and well
16 characterized events, and we are also looking into a
17 sentinel reporting system. Rather than having the universe
18 of hospitals report to us, we are working on establishing a
19 subset of hospitals who are well trained, well informed
20 about recognizing medical device issues, so that we can
21 obtain much more timely and higher quality reports.

22 We are also working on submission of reports
23 electronically. Today, we get them hard copy. We are
24 looking to integrate trend analyses with the quality system
25 regulations, and we are also in the process of exchanging

1 reports internationally and globally.

2 Under postmarket surveillance, I have mentioned
3 there are a wider variety of design approaches that we
4 should choose from. There should be more collaboration with
5 industry and the clinical community, and there should be
6 expanded access to relevant data sources.

7 That finishes my brief talk, and I will take any
8 questions if there are any.

9 DR. A. KALLOO: Any questions?

10 DR. DONATUCCI: I just have one question. How
11 many devices have actually been recalled under the
12 postmarket registry program? In other words, how many times
13 --

14 DR. GROSS: Have we instituted postmarket
15 surveillance?

16 DR. DONATUCCI: No, that you have instituted, but
17 that has resulted in the disapproval or revocation of
18 approval of a device.

19 DR. GROSS: I think it's fair to say never. I am
20 not sure about the PMA side of the house, but I don't think
21 it has ever resulted in a product withdrawal, and somebody
22 on the OD side can correct me if I am wrong.

23 With regard to the Section 522 authority, that is
24 a relatively new program, and it underwent significant
25 changes last year, so we have a very brief history, and it

1 has not resulted in any product withdrawals.

2 The purpose, if I didn't make it clear, is not
3 really to recall a product. The purpose is to set up
4 studies to address either "for cause" issues or potential
5 issues about the safety of a product.

6 DR. DONATUCCI: Right, but the public health
7 question ultimately is that a device was approved and placed
8 into use before an unanticipated problem arose. I mean I am
9 thinking of an analogous situation to drugs, such as the
10 anti-obesity drugs that were then pulled because of the
11 possible cardiac toxicity.

12 So, as of today, there is no analogous situation,
13 no device has actually be subject to that?

14 DR. GROSS: Not under those authorities. We
15 recall products under different mechanisms, but not under
16 those authorities, but let me give you a more concrete
17 example. Polyurethane foam-coated breast implants. They
18 were marketed a few years back, and some years into its
19 marketing, there were questions raised about its possible
20 carcinogenicity based on animal studies.

21 We ordered the company to do a study to help
22 resolve that issue, and they did a small-scale study
23 involving humans, blood testing and urine testing, and the
24 upshot of that study was that there was no significant risk
25 of carcinogenicity based on those data.

1 So, in that instance, it helped reassure us that
2 at least for that particular issue and for that particular
3 product, there was no long a major public health concern.
4 So, that is one concrete example. Of course, it didn't
5 result in any product withdrawal.

6 DR. DONATUCCI: I guess the thrust behind my
7 question is that regardless of whether it's PMA 522 or other
8 mechanism, the process that you have in place now for device
9 approval has served the public well. There hasn't been
10 major problems that have not been identified through this
11 process. Am I correct in that assumption?

12 DR. GROSS: Well, I think it has served us well,
13 and you still have the authority to conduct these condition
14 of approval studies. There are several other mechanisms by
15 which we monitor products. I alluded to one, the Medical
16 Device Reporting mechanism where we received adverse event
17 reports, and there are multiple things that we can do based
18 on those adverse event reports.

19 One of them -- maybe I should bring the slide back
20 up -- is ordering additional postmarket studies. The other
21 things we can do is we could directly inspect a firm, we can
22 ultimately seize the product, we can ultimately recall the
23 product, and this is absent any postmarket study.

24 DR. DONATUCCI: Those are what you can do. My
25 question actually was how often have you actually done that.

1 DR. GROSS: Well, absent a postmarket study, we
2 conduct recalls at least -- I am talking about the entire
3 agency -- I know for a fact several thousand a year. This
4 is absente postmarket studies. This is using other
5 mechanisms by which we surveil products.

6 The agency, as a whole, including drugs and
7 biologics and devices, conduct several thousand recalls a
8 year.

9 DR. DONATUCCI: I guess the thrust of my question
10 again is devices and how often does that happen.

11 DR. GROSS: Devices, I wish I had the exact
12 numbers, but I believe several hundred. I can clarify that
13 if anybody else has more current information, but it is a
14 substantial number.

15 DR. A. KALLOO: Any other questions?

16 DR. HUNTER: I have one. Having been a panel
17 member for a number of years, I have helped recommend
18 postmarket approval studies, and I am wondering what your
19 routine is to help check on those, and then I think some of
20 them are commerce. I am now looking back, and the
21 marketplace is very shrewd at finding a device that although
22 it's not dangerous, is no longer effective, and if you have
23 a system in place to say, hey, enough, or have a review and
24 say enough, we can stop these studies, or do you have a
25 routine way of doing that, because it would be cumbersome on

1 the agency to continue every study that we recommend.

2 DR. GROSS: Well, there is a mechanism, at least
3 on the PMA side, where they get annual reports, and they are
4 required to look at the information submitted on these
5 interim reports, and basically follow through to make sure
6 that those studies are complete.

7 We are starting a process right now on reviewing
8 how well that process works. Now, on the 522 side of the
9 house, a related authority, as you can gather, we have
10 changed the program significantly because of the statutory
11 changes. I mentioned the 1990 and 1997 version.

12 So, we have a limited history with the new
13 approach, but our intent is, as you say, is to monitor these
14 studies to see if they are being conducted, to see how
15 useful they are ultimately, and to change our approach if
16 that doesn't work.

17 DR. BENNETT: Following up on Craig's issues, and
18 being the industry rep, I understand that the annual reports
19 are done, however, I would encourage you and the agency to
20 really fine-tune that as rapidly as possible.

21 I have rather direct experience in a very
22 prolonged postmarket study that will never, ever be able to
23 be completed on a product that has been on the market for
24 almost a decade, and going back to the issue that Craig
25 brought up, there are other mechanisms, and I would behoove

1 the FDA to try to step in and when you find and realize that
2 a postmarket approval study really is not adding anything,
3 then, be proactive rather than wait for the study to be
4 completed.

5 DR. GROSS: I would second that. You should be
6 aware of reengineering efforts that have been going on
7 within the center, and there is one initiated recently on
8 postmarket reengineering, and that is one of the topics for
9 the reengineering.

10 DR. BENNETT: If you need a specific example, I
11 will be more than happy to give it to you.

12 DR. GROSS: I am sure you would and I would
13 appreciate that.

14 DR. A. KALLOO: Thank you, Dr. Gross.

15 Next, Don St. Pierre will bring us up to date on
16 the progress made on matters previously presented before the
17 panel.

18 Don.

19 **Donald St. Pierre**

20 MR. ST. PIERRE: Good morning. I am Donald St.
21 Pierre, the Branch Chief of the Urology and Lithotripsy
22 Devices Branch. As is customary, I will give a brief update
23 regarding our past panel meetings, which is not terribly
24 customary, I am going to actually follow a script this time.

25 Our last meeting was held on October 29, 1998. At

1 this meeting the panel made a recommendation of approval
2 with conditions on a PMA Supplement from Cypress Bioscience,
3 Inc., for an extracorporeal immunoadsorption device called
4 the ProSORBA column indicated for use in the therapeutic
5 reduction of the signs and symptoms of moderate to severe
6 rheumatoid arthritis in adult patients with long-standing
7 disease who have failed or are intolerant to disease-
8 modifying anti-rheumatic drugs. FDA agreed with the panel's
9 recommendation and issued an approval order on March 15,
10 1999.

11 I would now like to update you on some other
12 activities that were subject to earlier panel meetings.
13 First, on July 30, 1998, the panel made a recommendation to
14 down-classify extracorporeal shock wave lithotripters from
15 Class III to Class II and also provided recommendations on a
16 special controls guidance document for extracorporeal shock
17 wave lithotripters.

18 This was an FDA-initiated down-classification.
19 FDA agreed with the panel's recommendations and issued a
20 proposed rule on February 8, 1999, to down-classify these
21 devices. On the same date, FDA also issued a Level 1 draft
22 guidance document in accordance with our internal good
23 guidance practices. The comment period on these documents
24 ended on May 10. We are in the process of addressing the
25 comments and preparing the final rule and final guidance

1 document.

2 Going back a little further, on February 12, 1998,
3 a closed panel meeting was held to discuss a product
4 development protocol, commonly referred to as a PDP, for
5 American Medical Systems' penile inflatable implants.

6 I am pleased to announce that the company
7 completed their PDP and was given marketing approval on
8 November 2, 1998. This represents the first ever completed
9 PDP for the agency and will ensure the continued
10 availability of these types of products when the final rule
11 is published calling for PMAs or PDPs.

12 For those of that are unfamiliar with the PDP
13 process, it is an approval process that has always been in
14 the regulation, but has never been used successfully until
15 now. As part of CDRH's reengineering efforts, this process
16 was given new life. For more information on the PDP
17 process, I suggest that you check out CDRH's web site.

18 The next couple of notable device approvals that I
19 will discuss involve implantable stimulators. Although not
20 subject to a previous panel meeting, I mention these because
21 the agency used guidance that was provided by the panel in a
22 previous panel meeting.

23 This panel met on August 6, 1997, to provide
24 recommendations on Medtronic's Implantable Sacral Nerve
25 Stimulator for the treatment of urinary urge incontinence in

1 patients that failed or could not tolerate more conservative
2 treatments.

3 Based on the panel recommendations, FDA approved
4 this device on September 29, 1997. Subsequent to that
5 approval, Medtronic submitted a PMA supplement to expand the
6 indications to include urinary retention and treatment of
7 patients with significant symptoms of urgency/frequency.

8 The agency determined that based on the panel's
9 deliberations at the August 6, 1997, panel meeting on the
10 original PMA application provided sufficient guidance and we
11 did not bring this before another panel. The device with
12 the expanded indications was approved on April 15, 1999.

13 The agency has also approved two humanitarian
14 device exemptions for an implantable stimulator. Like the
15 PDP, the HDE is another fairly new program which is directed
16 at devices that treat conditions affecting less than 4,000
17 patients a year.

18 This is CDRH's equivalent to orphan drugs. An HDE
19 requires that the sponsor demonstrate that their device is
20 safe and has probable benefit.

21 FDA used the knowledge gained from the August 6,
22 1997, panel meeting and applied it to the review of
23 NeuroControl Corporation's VOCARE Bladder system which is
24 indicated for the treatment of patients who have clinically
25 complete spinal cord lesions with intact parasympathetic

1 innervation of the bladder and are skeletally mature and
2 neurologically stable, to provide urination on demand and to
3 reduce post-void residual volumes of urine.

4 The VOCARE system was approved on December 28,
5 1998. NeuroControl Corporation submitted another HDE to add
6 a secondary indication to aid in bowel evacuation. This
7 secondary use was approved on February 19, 1999.

8 I would now like to follow up on a couple of
9 issues that Dr. Gross just discussed regarding two specific
10 post-approval studies that have been completed in urology.

11 As you may know, in December of 1988, the panel
12 recommended that all original PMA approvals for
13 extracorporeal shock wave lithotripters have as a condition
14 of approval, a requirement that a post-approval study be
15 conducted to study the relationship between lithotripsy and
16 hypertension.

17 The condition of this post-approval study
18 requirement has resulted in a labeling change for
19 extracorporeal shock wave lithotripters that changed the
20 statement that the risk of hypertension is unknown to the
21 statement that hypertension is not a long term risk of
22 lithotripsy.

23 This was further emphasized at last year's panel
24 meeting on the down-classification of extracorporeal shock
25 wave lithotripsy.

1 The second successful completion of a post-
2 approval study involves a device for the treatment of BPH.
3 On May 3, 1996, FDA approved EDAP Technomed's PMA for the
4 Prostatron which is a microwave thermal therapy system for
5 treating BPH.

6 This device was discussed at a panel meeting on
7 October 20, 1995, and the panel recommended approval with
8 conditions. One of the conditions was the completion of a
9 post-approval study to assess the long-term effects, that
10 is, five year years posttreatment, including durability and
11 re-treatment rates.

12 The sponsor completed the study and modified their
13 labeling to include five-year follow-up data. Both of these
14 studies demonstrate the benefits of a well-thought-out post-
15 approval study.

16 This concludes my update on past panel activities.

17 Thank you.

18 DR. A. KALLOO: Thank you. Any questions for Don?

19 If there is anyone else wishing to address the
20 panel, please raise your hand and you may have an
21 opportunity to speak.

22 [No response.]

23 DR. A. KALLOO: Since there are no other requests
24 noted, we will now proceed to the open committee discussion
25 of the premarket approval for P980053 Advanced UroScience

1 Durasphere (urethral bulking agent) as indicated for the
2 treatment of stress urinary incontinence due to intrinsic
3 sphincter insufficiency. This device is injected into the
4 urethral submucosa under endoscopic vision to achieve
5 urethral bulking and coaptation.

6 I would like to remind public observers at this
7 meeting that while this portion of the meeting is open to
8 public observation, public attendees may not participate
9 except at the specific request of the panel.

10 The first speaker for the sponsor is Karen
11 Peterson.

12 I was just told that we have more panel members,
13 Dr. Deitrick and Dr. Steinbach. If you could please
14 introduce yourself, your specialty, and your voting status,
15 please.

16 DR. STEINBACH: My name is Joseph Steinbach. I am
17 at the University of California at San Diego. I am an
18 engineer/biostatistician, and my voting status, I am a panel
19 member, I vote.

20 DR. DEITRICK: I am Richard Deitrick, Chairman of
21 the Department of Ob-Gyn at Mercy Hospital in Pittsburgh.

22 DR. A. KALLOO: And your voting status?

23 DR. DEITRICK: Panel member, yes.

24 DR. A. KALLOO: The first speaker for the sponsor
25 is Karen Peterson.

1 I would like to remind the speakers please
2 disclose whether they have financial interests in any
3 medical device company and, if so, please state your
4 financial interest.

5 **PMA P980053**

6 **Advanced UroScience Durasphere**

7 **(Urethral Bulking Agent)**

8 **Sponsor Presentation**

9 **Introductory Remarks and Product Description**

10 **Karen Peterson, M.S.**

11 MS. PETERSON: Good morning, Mr. Chairman and
12 distinguished panel members. My name is Karen Peterson and
13 I am the Vice President of Regulatory, Clinical and Quality
14 Affairs for Advanced UroScience.

15 [Slide.]

16 I would like to begin by introducing the other
17 individuals in attendance today who are representing
18 Advanced UroScience. Dr. Jeffrey Snyder, urologist from
19 Denver, Colorado, who is one of the investigators in the
20 clinical trial. Dr. Aaron Kirkemo, consulting urologist
21 from St. Paul, Minnesota. Attending from Advanced
22 UroScience today is Dean Klein, our President and CEO;
23 Richard Holcomb, our biostatistician, and Tina Wittchow, our
24 Clinical Research Manager.

25 [Slide.]

1 We are very pleased today to present our marketing
2 application for Durasphere Injectable Bulking Agent for the
3 treatment of stress urinary incontinence due to intrinsic
4 sphincteric deficiency, or ISD.

5 [Slide.]

6 Our presentation today will be conducted in four
7 parts. I will summarize the prevalence of urinary
8 incontinence, and I will provide you with the product
9 description. Richard Holcomb will present an overview of
10 the clinical trial study design and the protocol.

11 Dr. Jeffrey Snyder will summarize the injection
12 procedure and present the safety and effectiveness results
13 from the clinical trial. Then, I will present some
14 concluding remarks.

15 [Slide.]

16 Urinary incontinence is a common condition.
17 According to the U.S. Department of Health and Human
18 Services, urinary incontinence plagues 11 to 35 percent of
19 adults and at least half of the 1.5 million nursing home
20 residents in the United States.

21 At least 13 million American adults suffer from
22 some form of urinary incontinence, and 85 percent of them
23 are women. Urinary incontinence is generally recognized as
24 one of the major causes of institutionalization in the
25 elderly.

1 [Slide.]

2 Stress urinary incontinence due to ISD is a
3 condition where the bladder neck does not close properly.
4 Involuntary loss of urine occurs during a stress event such
5 as coughing, sneezing, laughing or other physical activities
6 that increase the abdominal pressure.

7 Durasphere is injected trans-urethrally under
8 direct visualization, through a cystoscope or endoscope into
9 the mucosal lining of the bladder neck or urethra.
10 Durasphere is injected using a commercially available
11 injection needle. Durasphere is designed to create
12 increased tissue bulk and subsequent coaptation of the
13 bladder neck or urethra to prevent involuntary loss of
14 urine. Here you can see the demonstration of the increased
15 tissue bulk.

16 [Slide.]

17 Durasphere is a sterile, injectable bulking agent
18 composed of pyrolytic carbon-coated beads suspended in a
19 water-based beta-glucan carrier gel. Durasphere is
20 dispensed in a commercially available, individually packaged
21 one-milliliter syringe.

22 [Slide.]

23 The size range of the beads is 212 to 500 microns,
24 which has been deliberately chosen to be well above any
25 known threshold for migration. Published studies in the

1 **Richard Holcomb, Ph.D.**

2 DR. HOLCOMB: Good morning. My name is Richard
3 Holcomb. I am a biostatistician for Advanced UroScience,
4 and I am pleased to present highlights of the study design
5 for the Durasphere clinical study.

6 [Slide.]

7 The goal of this IDE study was to evaluate the
8 safety, effectiveness, and performance of the Durasphere for
9 the treatment of stress urinary incontinence due to ISD in
10 male and female adults.

11 The specific objectives of the study include:

12 1. Evaluating the effectiveness of Durasphere in
13 improving the patient's incontinence over a one-year period
14 commencing with their first treatment.

15 2. Assessing the safety of Durasphere by
16 quantifying any adverse health effects during and after the
17 transurethral injectable procedure.

18 3. Comparing the safety and effectiveness of
19 Durasphere for the treatment of stress urinary incontinence
20 with the safety and effectiveness of the control.

21 [Slide.]

22 This study was designed as a multi-center, double-
23 blinded, randomized, controlled trial. Patients were
24 assigned to receive either the Durasphere or the market-
25 released control product, Contigen.

1 The randomization was one-to-one between
2 Durasphere and control and was stratified by the gender of
3 the subjects and blocked within clinical sites to achieve a
4 balance between study centers.

5 The study was a double-blind trial. Due to the
6 nature and treatment and anatomy involved, patients would be
7 blinded to the treatment they received. Treating physicians
8 could not be blinded, however, due to the differences in the
9 study material, because of the different appearance and
10 handling characteristics, as well as packaging. However,
11 study staff and non-treating physicians who performed the
12 follow-up evaluations were blinded to the therapy.

13 [Slide.]

14 The study had two primary efficacy endpoints.

15 The first endpoint was the change in the
16 continence grade score of the patient from baseline to the
17 12-month posttreatment interval time point. This endpoint
18 was used to determine the required sample size. A decrease
19 in the continence grade of one or more grades was considered
20 a success for purposes of evaluating this endpoint.

21 [Slide.]

22 The continence grades used for the study and
23 involved in the success criteria were defined by Stamey in
24 1979 and have been used frequently in incontinence studies
25 including the prior Contigen clinical trial.

1 This is a four-point scale from zero to 3, with
2 zero indicating a continent or dry status of the patient;
3 Grade 1, some loss of urine with increases in abdominal
4 pressure; Grade 2, a worsening of incontinence associated
5 with physical activities; and Grade 3, associated with total
6 incontinence and urine lost without any relation to activity
7 or position.

8 [Slide.]

9 The second primary efficacy endpoint for the study
10 was based on urine loss during pad weighing testing, and
11 also evaluated the improvement from baseline to 12 months
12 post-treatment.

13 [Slide.]

14 This pad weight endpoint was measured by
15 evaluating the urine loss of patients who underwent a
16 prescribed set of activities included in the protocol that
17 led to stress incontinence. This urine loss was quantified
18 through the use of pads, which were worn by the patients and
19 then weighed at the completion of the activities.

20 [Slide.]

21 The primary endpoint of safety was evaluated
22 through an analysis of morbidity and complication rates
23 associated with the use of Durasphere, and the evaluation of
24 those risks.

25 Safety was assessed by the physician through

1 physical examinations and by questioning patients
2 immediately post-injection and at all subsequent follow-ups.

3 Symptoms and complications were recorded for all
4 patients. The investigators were instructed to report any
5 symptom or adverse event, and to rate each experience for
6 the intensity, duration, possible cause, and eventual
7 outcome of that adverse event. All reports of adverse
8 experiences were reviewed and classified additionally by the
9 nature and severity of the event, as well as the
10 relationship of the event to the device or the treatment
11 procedure.

12 [Slide.]

13 Investigators classified these adverse events as
14 mild, moderate, or severe: mild events being defined as
15 those requiring minimal medical treatment; moderate events
16 being associated with temporary disability or other medical
17 or surgical interventions; and severe events defined as one
18 that were associated with life-threatening episodes.

19 [Slide.]

20 A number of secondary endpoints were also
21 evaluated statistically in the study. These included the
22 following:

- 23 1. The number of patients who had improved in
24 continence grade at follow-ups before and after one year.
- 25 2. The number of patients who were dry, that is,

1 an incontinence grade of zero at each follow-up interval.

2 3. The total number of treatments required
3 including re-treatments.

4 4. The volumes of the Durasphere and control
5 materials injected.

6 5. Changes in an incontinence-specific validated
7 quality of life instrument.

8 [Slide.]

9 Initial sample sizes were calculated for
10 evaluation of the primary study endpoint of incontinence
11 grade change based on the Blackwelder approach through
12 equivalence trials, with a design criteria of a Type 1 error
13 alpha of 0.05 and an 80 percent statistical power. This led
14 to an estimate of 232 patients to be followed for one year.

15 [Slide.]

16 Summary statistics were calculated for all study
17 variables. These included the common summary measures of
18 mean, s, standard deviations, standard errors, and the like.

19 Differences in continuous variables between the
20 treatment groups or between phases of the study were
21 evaluated using two-sample tests, such as Student's t-tests.
22 Within-patient differences were evaluated using paired
23 tests, and where there was evidence of non-normality of any
24 of the responses, appropriate nonparametric tests were used
25 or evaluated including Wilcoxin and Mann-Whitney tests.

1 Evaluations of more than two independent groups,
2 such as evaluation of clinic differences, employed analyses
3 of variances or their nonparametric equivalent. Comparisons
4 of categorical variables employed Fisher's Exact Tests,
5 thereby not depending on the distribution of the responses,
6 and in either the report or subsequent communications with
7 the FDA, multiple analyses, multiple regression analyses,
8 and other multivariable analyses were performed including
9 logistic regressions and repeated measures analyses.

10 Unless otherwise indicated, all statistical tests
11 were two-sided, with p-values of less than 0.05 or equal to
12 0.05 considered evidence of statistical significance.

13 [Slide.]

14 Upon enrollment into the study, baseline patient
15 and medical history data relevant to the diagnosis of stress
16 urinary incontinence were collected. At baseline and
17 follow-up visits, data were also collected on the results of
18 laboratory blood and urine testing, abdominal leak point
19 pressure testing, pad weight tests, seven-day voiding
20 diaries, and Quality of Life instruments.

21 In addition to the assessment of changes in
22 continence grade at scheduled follow-up visits, data were
23 recorded on any procedure- or urology-related symptoms, side
24 effects, and safety issues seen by the physician or reported
25 by the patient.

1 A maximum of four re-treatments was allowed in the
2 study, consistent with the labeling for the control device.
3 Re-treatment was to occur when the patient had not improved
4 or when the investigator believed that another treatment
5 would be beneficial to the patient.

6 [Slide.]

7 At this point, I would like to introduce Dr.
8 Jeffrey Snyder from Denver Colorado, who will summarize the
9 injection procedure and the clinical study results.

10 Thank you.

11 **Injection Procedure and Clinical Study Results**

12 **Jeffrey Snyder, M.D.**

13 DR. SNYDER: Good morning, Mr. Chairman and panel
14 members. I am very pleased to have this opportunity to
15 advance what I believe is a safe and effective treatment for
16 stress urinary incontinence due to intrinsic sphincter
17 deficiency. The urology community anxiously awaits an a.
18 non-immunogenic urethral bulking agent.

19 First, let me disclose that I have no financial
20 ties with Advanced UroScience other than that as a clinical
21 investigator and as a consultant.

22 [Slide.]

23 I am going to begin my presentation today by
24 showing you a video of an actual injectable procedure that
25 was performed from one of our sites that occurred during the

1 clinical trial, to demonstrate the simplicity of this
2 injectable technique.

3 This is an example of a cystoscopic view looking
4 into the bladder. At the 5 o'clock position, we see the
5 injection needle. This is quite an intuitive procedure for
6 any urologist or gynecologist who performs cystoscopic
7 procedures. We have an open bladder neck. The needle is
8 advanced into the submucosal region. The needle has been
9 primed with the Durasphere, and you can see, with
10 infiltration and implantation, you get bulking of this area
11 in the submucosal region, a bulk mass effect, and you see
12 closure of the bladder neck region.

13 This is quite a simple procedure with a very short
14 learning curve, and this is quite easily accomplished and
15 was demonstrated by all our sites, and you can see closure
16 of the bladder neck.

17 It is very interesting to look at the device. As
18 you can see, although there is a puncture site here with the
19 implants, it does not, because of the impregnation in the
20 beta-glucan gel, does not leak out of this area, and it is
21 surmised and believed that this will be something that is
22 important for the long-term durability of this very
23 biocompatible and non-immunogenic implant.

24 A second puncture site is created at the 7 o'clock
25 position. The sites of puncture are very operator-dependent

1 and what we are looking for is just coaptation and decrease
2 of this lumen in the bladder neck.

3 One starts very proximally in the urethra and
4 works more distally. This is an analogous situation in the
5 male patient, as well, and this is obviously a female
6 patient.

7 [Slide.]

8 In summary, this minimally invasive, simply
9 injection procedure takes less than a half-hour and is
10 easily accomplished in an outpatient setting. For
11 physicians experienced with injectable bulking agents, this
12 procedure is routine and quite intuitive to begin.

13 [Slide.]

14 In June 1996, Advanced UroScience began this
15 investigational study of Durasphere injectable bulking
16 agent. A total of 377 patients were injected with either
17 the Durasphere or the control bulking agent at 10
18 investigational centers. The data includes all patients
19 treated in the study as of December 1, 1998, and all follow-
20 up data received up until May 21, 1999.

21 This IDE study was open to both men and women. Of
22 these 377 patients, 355 patients were female and 22 were
23 male. Based upon anatomical and etiologic differences in
24 their incontinence, it was expected that the treatment
25 outcomes would be gender specific. Thus, study results were

1 reported separately for men and for women.

2 The male patients experienced less improvement
3 than the female counterparts. However, these improvements,
4 as well as the overall clinical results, were similar in
5 male patients between Durasphere and the control.

6 I will now be presenting the results from the
7 female population in the study.

8 The Durasphere female population were followed in
9 the study for a mean of 10.7 months with a cumulative study
10 time of 1,997 months. As required, at least 232 female
11 patients were evaluated at one year post-injection.

12 [Slide.]

13 This busy slide displays the baseline
14 characteristics of the patients receiving Durasphere and the
15 control product. There was no significant difference
16 between the Durasphere and the control patients for any of
17 the baseline variables. This was a very well matched group
18 of patients.

19 [Slide.]

20 The first primary endpoint is the percentage of
21 patients improved by greater than or equal to 1 continence
22 grade based upon the Stamey system at 12 months. As shown
23 in the slide, 66.1 percent of Durasphere patients and 65.8
24 percent of the control patients demonstrated an improvement
25 in the continence grade of greater than or equal to 1 at 12

1 months. No significant difference was observed between
2 Durasphere and the control group.

3 This primary endpoint was also evaluated using the
4 Blackwelder method, in which the Durasphere device was found
5 to be equivalent to that of the control, with a p-value of
6 0.007.

7 [Slide.]

8 The second primary endpoint is the change in pad
9 weight from baseline to 12 months. As shown in the slide,
10 the mean change or decrease in weight in pad weight from
11 baseline to 12 months was 27.9 grams in the Durasphere group
12 and 26.4 grams in the control group. No significant
13 difference was observed between Durasphere and the control.

14 In summary, what we can say is there is no
15 significant difference in the two primary efficacy endpoints
16 between Durasphere and the control group. It is therefore
17 concluded that the effectiveness objective of the study has
18 been met and that Durasphere's effectiveness is equivalent
19 to that of the commercially available control group.

20 [Slide.]

21 I would now like to present the results of the
22 safety data of the primary safety endpoints, namely adverse
23 events experienced during the clinical trial. It is
24 important to point out that Advanced UroScience included all
25 symptoms and observations reported on the case report forms

1 regardless of whether or not they were related to the study
2 product. Many of the events were unrelated to the study,
3 but were included by the sponsor for completeness.

4 This slide demonstrates all of the mild, moderate,
5 and severe adverse events by severity distribution. The
6 mild category consisted of 87.6 percent of Durasphere
7 events, 11.6 percent as moderate, and 0.8 percent of severe
8 events.

9 The three events considered severe for the
10 Durasphere patient included patients with chest pain, renal
11 failure, and myocardial infarction. All three events were
12 deemed unrelated to the device or to the procedure by the
13 clinical investigators.

14 There was no significant difference seen in the
15 distribution of severity of events between Durasphere
16 patients and the control group.

17 [Slide.]

18 This slide shows the incidence of the adverse
19 events that were reported by 10 percent or more of the
20 Durasphere patients.

21 There were a total of 31 different categories of
22 adverse events reported during the study. Once again, there
23 was no significant difference in the incidence of events
24 between the Durasphere and the control group for 29 of the
25 31 groups.

1 However, there was a significantly higher
2 incidence of urgency and acute urinary retention, defined
3 for duration less than seven days, for Durasphere for the
4 control patients, with the p-values of 0.002 and less than
5 0.001, respectively, and I will address these two different
6 categories in my next two slides.

7 [Slide.]

8 With regard to urinary retention, 30 Durasphere
9 patients experiences symptoms of acute urinary retention,
10 defined as inability to void or the sensation of incomplete
11 bladder emptying, following treatment.

12 Twenty cases were resolved after short-term
13 catheterization, and one case the treating physician chose
14 to remove 2 ml of material by aspiration in a transvaginal
15 fashion, thereby allowing the patient to void. Nine cases
16 resolved on their own without any intervention.

17 All cases of acute urinary retention were resolved
18 on an average of four days with a maximum of seven days
19 post-treatment. No untoward consequences were experienced
20 by any of these patients, nor was there any adverse impact
21 on continence improvement.

22 [Slide.]

23 With regard to the urgency issue, 44 Durasphere
24 patients experienced urgency some time in the study.
25 Thirteen of these patients reported symptoms of urgency

1 prior to entering the study, therefore, we are discussing 31
2 patients who experienced de novo or new onset of urgency.

3 The vast majority of these urgency symptoms that
4 were reported were resolved and required limited medical
5 intervention. Eighteen cases resolved on their own without
6 any intervention, and 12 of the remaining 13 were resolved
7 with medication.

8 All urgency events treated with medications were
9 considered mild. Twelve of the 13 events resolved on an
10 average within 57 days. One patient remains on Ditropan, a
11 bladder antispasmodic, for the treatment on urgency at the
12 time the database was closed in May.

13 It is certainly worth noting that the proportion
14 of Durasphere urgency events that were resolved were
15 significantly better than that of the control group. As of
16 the time of the database closure, 90 percent of the urgency
17 events for Durasphere were completely resolved as compared
18 to 65 percent of the urgency events for the control group.
19 The p-value for this difference was 0.021.

20 [Slide.]

21 The mean duration and resolution of all adverse
22 events are displayed on the slide.

23 The duration of an adverse event was calculated by
24 subtracting the onset date from the date that the event was
25 documented to be resolved. As shown in this slide, the

1 overall mean duration of all adverse events was
2 significantly lower or better clinically for Durasphere
3 compared to the control group, with a p-value of 0.032.

4 Overall, 91 percent of the Durasphere events were
5 resolved as of the database closure as compared to 87
6 percent of the control group events.

7 [Slide.]

8 Our adverse event summary. This slide
9 demonstrates the overall adverse event profile of Durasphere
10 patients and the control group patients is actually quite
11 similar. This is based on the evaluation of the four
12 adverse events attributed as just discussed - the severity,
13 the incidence, duration of the events, and resolution of the
14 events.

15 There was no difference between groups in the
16 severity of the events. If you multiply the number of
17 events by the duration of events you obtain total adverse
18 event days. Although the number of events was higher for
19 Durasphere, the duration was longer for the control group.
20 Therefore, the combined total adverse event days was similar
21 between the two groups.

22 Finally, there was no difference between groups in
23 the resolution of these events. We conclude, therefore,
24 that the overall adverse event profile is similar between
25 Durasphere and the control group.

1 [Slide.]

2 Looking at our secondary endpoints now, in the
3 next few slides I will summarize the secondary endpoint
4 results of the study. This slide demonstrates and displays
5 the improvement in continence grade at the various follow-up
6 periods of one month, three months, six months, 12 months,
7 and 18 months for the Durasphere patients.

8 As can be easily seen by this bar graph, the mean
9 continence grade was significantly and consistently improved
10 from baseline to follow-up, all the way across all the time
11 periods for the Durasphere patients. The p-value was 0.001.

12 Interestingly, at the 12-month period, the mean
13 continence rate for Durasphere was significantly improved
14 from 1.8 at baseline to 0.97. This represents a 48 percent
15 improvement in the mean continence grade.

16 No significant difference in mean change of
17 continence grade was observed between Durasphere and the
18 control group at any of the follow-up visits.

19 Secondary endpoints improvement of greater or
20 equal to one continence grade.

21 [Slide.]

22 This table displays the proportion of Durasphere
23 and control group patients who have improved by one or more
24 continence grades from baseline to the time of their follow-
25 ups. No significant difference was observed between the

1 proportion of Durasphere and control group patients who
2 demonstrated improvement by greater than or equal to one
3 continence grade at anytime in the follow-ups. These are
4 very equivalent groups at all follow-up areas up to 18
5 months.

6 Previous studies on the control population
7 reported the proportion of patients demonstrating
8 improvement at some time during the study. For comparative
9 purposes, 90 percent of Durasphere patients and 89 percent
10 of the control patients demonstrated an improvement of equal
11 to or greater than one continence grade at some time during
12 the study.

13 [Slide.]

14 There was no significant difference in the
15 proportion of patients who achieved a continence grade of
16 zero, defined as dry, between the patients in the two groups
17 at any time in the follow-up visits.

18 [Slide.]

19 This slide depicts pad weight test by time. This
20 next figure displays the improvement in pad weight of the
21 Durasphere population in the time periods, and what we can
22 observe is a decrease in pad weight test at all parameters
23 of one month through 18 months.

24 The mean pad weight was significantly improved or
25 reduced from baseline to follow-up at all time periods for

1 Durasphere patients, with a p-value of less than 0.001.
2 These results parallel the graph recently shown for
3 improvement for continence grade.

4 The mean pad weight for Durasphere patients was
5 significantly improved from 47.2 grams at baseline to 19.3
6 grams at the 12-month period. This also represents a 59
7 percent reduction in pad weight at 12 months.

8 No significant difference in pad weight was
9 determined between the Durasphere group and the control
10 group.

11 [Slide.]

12 Patients were required to complete a voiding diary
13 once week prior to each follow-up visit. This figure
14 displays the improvement in incontinence episodes per week
15 by time periods for the Durasphere population.

16 The mean number of episodes per week was
17 significantly improved from baseline to follow-up at one,
18 three, six, and 12 months for the Durasphere patients, with
19 a p-value of 0.001.

20 I want to bring your attention to the improvement
21 at all these time parameters and the similarity in the
22 parameters they were measuring in the secondary endpoints.
23 There is quite a bit of consistency in this product.

24 At 12 months, the mean number of episodes per week
25 was significantly improved from 20.8 episodes per week to

1 10.2 episodes per week at 12 months. This represents an
2 improvement of 51 percent.

3 No significant difference in change in number of
4 incontinence episodes from baseline to follow-up was
5 observed during this trial between Durasphere and the
6 control group.

7 [Slide.]

8 This slide depicts Quality of Life and the Quality
9 of Life survey scores that were determined during the time
10 periods of the Durasphere study population. The mean
11 incontinence Quality of Life score was significantly
12 improved from baseline to follow-up at all time periods for
13 the Durasphere patients. The p-value was less than 0.001.

14 At 12 months post-treatment, the mean score of
15 Durasphere patients was significantly improved from 55.5 at
16 baseline to 73.7 at the 12-month period. This represents an
17 improvement of symptoms of 33 percent in the incontinence
18 Quality of Life score at 12 months.

19 No significant difference in the mean change of
20 incontinence Quality of Life scores from baseline to follow-
21 up was observed between the two groups at any of the follow-
22 ups.

23 [Slide.]

24 Number of injections. The distribution of the
25 total number of treatments that each patient received during

1 the study is displayed on this graph. The mean number of
2 Durasphere injections per patient during the clinical trial
3 was 1.69. There was no significant difference in the number
4 of treatments between the Durasphere patients and the
5 control patients.

6 [Slide.]

7 Injection volume. This table represents the mean
8 volume of material injected at the initial treatment for
9 Durasphere and control patients, as well as the total volume
10 of material injected for patients during the study.

11 The Durasphere patients had a mean of 4.8 ml of
12 material injected at the initial injection as compared to
13 the control group of 6.2 ml. The total mean volume of
14 material injected during the study was, on average, 7.6 ml
15 for the Durasphere patients and 9.6 ml for the control
16 patients. Thus, Durasphere patients had significantly less
17 material injected at the initial injection time, as well as
18 total injection material, less was injected during the
19 study. The p-value of this was 0.001. Whether this
20 difference is clinically significant still remains to be
21 determined.

22 [Slide.]

23 Durability. One of the potential advantages of
24 Durasphere over the control group material is the fact that
25 Durasphere beads are non-absorbable, whereas, collagen is

1 absorbed by the body over time. In theory, one would expect
2 the Durasphere implants to be more durable.

3 My final two slides give some insight into the
4 durability of Durasphere compared to the control.

5 The fact that the re-treatments were allowed to
6 occur throughout the study confounds the results of the
7 durability tests. If one were to evaluate the patients who
8 received a single injection during the study, it would show
9 how these patients endured over time without additional
10 treatments.

11 This slide shows the improvement in continence
12 grade by follow-up for all patients who received a single
13 injection during the study for both Durasphere and control.
14 At one year post-treatment, 83.7 percent of Durasphere
15 patients as compared to 71.4 percent of control patients
16 were improved by greater than or equal to one continence
17 grade compared to baseline. Remember that these are
18 patients who received only one single treatment. The p-
19 value for this difference is 0.166, which is suggestive but
20 clearly not significantly different.

21 [Slide.]

22 My final slide shows the results as if were to
23 analyze the data in a slightly different way, or the
24 retrospective way, that is looking at improvement one year
25 after the last injection was received and looking back.

1 This includes the evaluation of the two primary
2 efficacy endpoints, which were improvement in continence
3 grade and pad weight a 12 months post-treatment. Both
4 continence grade and pad weight were significantly improved
5 from baseline to follow-up for Durasphere patients, and the
6 results are found to be equivalent to that of the control
7 group.

8 For the primary safety endpoint, few differences
9 were found between Durasphere patients and the control group
10 patients in the severity, incidence, duration, and
11 resolution of all adverse events. No new or unique safety
12 issues were identified for Durasphere.

13 No significant differences were found between the
14 Durasphere patients and the control group patients in any of
15 the secondary endpoints at any of the follow-up intervals.

16 Lastly, the durability of improvement for
17 Durasphere was found to be not significantly different from
18 that of the control group, however, the results are
19 suggestive of potential longer term durability of Durasphere
20 compared to the control material.

21 [Slide.]

22 The following conclusions from the study have been
23 drawn:

24 1. Durasphere injection is safe to use for
25 treating the symptoms of stress urinary incontinence. No

1 safety issues arose that limit its application when used
2 according to its instructions for use.

3 2. Durasphere injection has been effective in
4 reducing stress urinary incontinence as measured by
5 improvement in continence grades, pad weight tests,
6 incontinence episodes, and validated Quality of Life
7 instruments.

8 3. The effectiveness of Durasphere was found to
9 be equivalent to that of the commercially available control
10 device in a prospective, controlled, randomized clinical
11 trial.

12 This study has demonstrated the safety and
13 effectiveness of Durasphere in the treatment of stress
14 urinary incontinence due to ISD.

15 I thank you very much for your attention.

16 DR. A. KALLOO: I had a specific question. Any
17 questions from the panel? The question I had, was there a
18 relationship between side effects, specifically, urinary
19 retention and the volume or frequency of injections?

20 MS. PETERSON: We looked at that, and there is no
21 relationship between those two.

22 DR. STEINBACH: Question. How much of the bulk
23 was due to the pyrolytic graphite at the day of injection or
24 the instant of injection and at long-term follow-up, because
25 the handout we read said that most of the bulk is being

1 provided by tissue reaction rather than the pyrolytic
2 graphite itself? I may have misread the handout.

3 DR. SNYDER: If I can repeat your question, you
4 want to know, the bulking effect, how much was due to the
5 actual pyrolytic beads as opposed to the transfer agent
6 beta-glucan?

7 DR. STEINBACH: Right.

8 DR. SNYDER: The percentage of pyrolytic beads
9 that is infiltrated in the beta-glucan is right now
10 proprietary information, and I am sure will be opened up
11 later on.

12 DR. STEINBACH: It might take studies that you
13 couldn't do in people to know how much is pyrolytic and how
14 much is tissue material at 12 months, or is that also
15 proprietary?

16 DR. SNYDER: No, I don't believe so. I think that
17 is an excellent comment, and I think that information
18 actually will be available at some point in the very near
19 future in laboratory animals.

20 DR. DIAMOND: I think that is a very good
21 question. I read that also. I thought the reason that you
22 have the bulking was collagen growth stimulated by beta-
23 glucan, and some of what I read talked about how beta-glucan
24 is also used in wound healing, but again, from the
25 presentation, what I heard was that the bulking is due to

1 the particles.

2 So, I think a question of which it is, is
3 important, particularly if you deal with issues of
4 durability and why it is there and why repeated injections
5 might have been necessary if it is due, in fact, to the
6 particles.

7 DR. SNYDER: Well, I don't believe that one can
8 absolutely say, there is clearly no data to say that it is
9 the particles versus the transfer agent, the beta-glucan,
10 that is providing the bulking. I think it is probably safe
11 to say at this point, with the science that we have, that it
12 is a combination of both agents and possibly the reduction
13 in the effectiveness following one injection may very well
14 be due to absorption of beta-glucan.

15 DR. VERTUNO: Do you have an explanation for the
16 increased incidence of short-term urinary retention compared
17 to control?

18 DR. SNYDER: We looked at those issues because
19 clearly, there was a difference in those 2 out of 31 groups.
20 There were certain things that we looked at. We looked at
21 anesthetic agents, first of all. A variety of anesthetic
22 agents were utilized during the procedure from local
23 anesthesia with lidocaine, lidocaine with epinephrine, up to
24 a more invasive general anesthetic. That analysis showed no
25 difference between anesthetic agent and the incidence of

1 urinary retention.

2 We do feel that possibly some of the incidence of
3 urinary retention was due to the size of the needle, which
4 is larger in the Durasphere group than the control, the
5 technique which takes a little bit longer than the control,
6 and irritation from the cystoscope.

7 DR. FOOTE: I understand through the protocol that
8 you did follow-up urodynamics at one year. Was there a
9 difference in the urodynamics in those patients who had
10 experienced the prolonged urinary retention or the bladder
11 irritative symptoms from the patients who did not?

12 Specifically, I am interested to know if those
13 patients at one year demonstrated a bladder outlet
14 obstruction.

15 MS. WITTCHOW: As shown on the urodynamics, we did
16 not show evidence of bladder outlet obstruction. In this
17 patient population, they had a lower post-void residual than
18 our general population of patients.

19 DR. SNYDER: Also, interestingly, there was --
20 which is consistent with the majority of the literature --
21 there was difference in Valsalva leak point pressure of
22 these patients, and, Dr. Foote, you had a very eloquent
23 article back in the mid-nineties in paraplegia, I believe,
24 which did show some increase in Valsalva leak point
25 pressure, but we did not show that in our population.

1 DR. A. KALLOO: Could the prior speaker identify
2 herself, please.

3 MS. WITTCHOW: My name is Tina Wittchow, and I am
4 the Manager of Clinical Research for the sponsor.

5 DR. HUNTER: Were any of the control group
6 patients injected with periurethral, like a spinal needle,
7 or was it all transurethral injection?

8 DR. SNYDER: This was purely a transurethral
9 procedure done via the cystoscope.

10 DR. HUNTER: Just some clinical questions. It
11 looks like that the gel doesn't leak out as well as the
12 control. Is that the experience of the investigators?

13 DR. SNYDER: Yes. I believe that, and that is
14 what I tried to demonstrate in the initial video. It
15 appears that although it takes a slight bit more effort than
16 the control to implant the device, one of the advantages is
17 there is also a decrease in the leakage rate post-treatment.

18 Another observation that we made is something
19 called urethral molding. Following the implantation of the
20 control group, if you were to catheterize the patient, you
21 tighten up the bladder neck in a very nice fashion with the
22 control, but when you catheterize the patient, and you look
23 back in with the cystoscope, you see that the area has
24 opened up slightly, there is a little bit of molding. It's
25 a softer material.

1 With the Durasphere implant, we did not find that
2 molding present at all.

3 DR. HUNTER: One investigator showed you can
4 actually aspirate the material out?

5 DR. SNYDER: This is a one-site, one-patient
6 treatment of what the investigator felt might possibly have
7 been an abscess causing urinary retention, and this was done
8 through a transvaginal route, aspirate of 2 ml. This is
9 certainly not something that we recommend on a routine basis
10 for patients.

11 DR. HUNTER: Did anyone experience rupture of the
12 submucosal bleb with either the control or the Durasphere?

13 DR. SNYDER: Yes, I think it is fair to say that
14 that occurs somewhat frequently depending upon the depth and
15 volume of implant that you put in no matter what type of
16 injectable you use, and I think the basic tenet would be to
17 go to another area that will capture the implant.

18 DR. HUNTER: So, your study included the rupture
19 because -- well, they just kept track of the total, and they
20 just put in whatever it took?

21 DR. SNYDER: Yes, absolutely.

22 DR. A. KALLOO: What were the indications for
23 repeat injections, how did you decide which patients you
24 were going to do a second and a third injection?

25 DR. SNYDER: At follow-up visit, the patients were

1 seen by the study coordinators and the blinded physician.
2 The normal parameters of quality of life and incontinence
3 pad weight tests in all the follow-ups, that were standard
4 in the protocol, were measured.

5 It was then determined based upon the patient's
6 desire and these tests, a discussion was made with these
7 people to decide who would be re-treated.

8 DR. HUNTER: Would you inject the material
9 routinely without doing a skin test? That is an open-ended
10 question.

11 DR. SNYDER: Are you talking about future use?

12 DR. HUNTER: Yes.

13 DR. SNYDER: Yes, we saw absolutely no
14 antigenicity or this implant, and were quite impressed by
15 it, and I think this is a major advantage.

16 DR. N. KALLOO: Did you exclude patients with
17 cystoceles or any other gross visible signs?

18 DR. SNYDER: According to the protocol, we did not
19 include patients with Grade 4 cystoceles or significant
20 cystoceles that were contributory to obstruction. So,
21 patients in the population did have Grade 1's, maybe Grade 2
22 cystoceles, and Grade 3's and 4's were eliminated.

23 DR. N. KALLOO: Were there any cures? I note that
24 you mentioned greater than one continence grade. What was
25 your absolute cure rate with absolute dryness?

1 DR. BENNETT: It was on one of the slides.

2 MS. PETERSON: Right.

3 DR. BENNETT: Between 20 and 25 percent, the same
4 in both groups.

5 MS. PETERSON: It was roughly a third at 12
6 months. Turn to page 36 of your clinical reports. It is
7 there.

8 DR. STEINBACH: I noticed two of the slides you
9 showed to the public with pad weight and with injection
10 volume, these parameters are normally tested with the t-
11 test, and you reported the p-value by the Fisher's Exact
12 Test on your slide. It's not that way in the handout.

13 DR. HOLCOMB: There were, as you rightly assert,
14 most of these tests of continuous measures were Student t-
15 tests unless there was some reason not to, example, non-
16 normal distribution of the data, but we had quite a large
17 sample size, so that wasn't an issue for us.

18 There were cases where there was classification of
19 patients, for example, in terms of severity of incontinence
20 or whenever, where it was appropriate.

21 DR. STEINBACH: Could it be a typo?

22 MS. PETERSON: The pad weight, we used a two-sided
23 Student's t-test.

24 DR. STEINBACH: It wasn't that way on the slide.

25 MS. PETERSON: Okay. If you look on page 38 of

1 your report.

2 DR. A. KALLOO: Could you tell us the data on the
3 male patients?

4 DR. SNYDER: I am sorry. Could you repeat that?

5 DR. N. KALLOO: Your results on male patients.

6 DR. SNYDER: Once again, it should be obvious that
7 our male population was quite small.

8 MS. PETERSON: That was included in your
9 appendices on the males. We do acknowledge that there was a
10 small sample size for the males, however, some males did
11 benefit, and there were no safety issues.

12 So, what we have done is in our labeling, we have
13 acknowledged that and we have a precaution statement that
14 reads like this: "The improvements in the male patients
15 experience were less than that of the females, but similar
16 to that of the commercially available control device." We
17 have that as a precautionary statement.

18 DR. A. KALLOO: And the incidence of adverse
19 effects in the males, were they any different even though
20 it's a small group?

21 MS. PETERSON: It's a very small group, and it is
22 your appendix, but you will see it is actually very
23 comparable to the females, if not less. So, there were no
24 new or safety issues there.

25 DR. HAWES: What did you learn from the repeat

1 injections when you went in to repeat the injection, what
2 was the appearance, and can you derive any information of
3 why the repeat injections failed?

4 The second question is did you reinspect anybody,
5 not just urodynamics, but actually reinspect anybody at the
6 end of the study period to look morphologically at what the
7 injection looked like?

8 DR. SNYDER: To answer your first question, which
9 was what were the observations of the clinical implanters on
10 reinjection, I think similar findings that we found with the
11 control group, which were there were several areas of
12 mucosal erosion where there was some denuded mucosa, where a
13 blebbed area of a mass had actually just busted open and
14 been excreted out in the urine.

15 In none of my patients -- and I injected 34
16 primary patients, I had a total of 70 patients of Durasphere
17 and controls -- did we find any beads left in the bladder in
18 any patients, which actually surprised me a little bit. I
19 was concerned that maybe some beads would be left in the
20 bladder, and this was never reported by any of the
21 investigators.

22 In other areas, we found the beads to be present
23 embedded in the submucosa with some effect, but there
24 appeared to be, one of the observations I made at
25 termination of primary treatment was what percentage of the

1 urethra did I close off, did I get 80 percent, 100 percent,
2 and at reinjection, there appeared to be no correlation
3 between the degree of closure that we made versus the degree
4 of continence.

5 So, in some patients that we got an 80 percent
6 closure of the urethra, who we anticipated would probably
7 need another injection, when we looked at the data, we saw
8 that some of those patients were quite dry, and other
9 patients where we had had 100 percent closure, at three
10 months, six months, 12 months, those patients required
11 reinjection.

12 As far as the second question -- does that
13 adequately answer your first one?

14 DR. HAWES: Yes.

15 DR. SNYDER: As far as the second question, all
16 patients at all follow-up visits underwent routine
17 examination, and there were no morphologic problems that
18 were visualized on vaginal pelvic examination.

19 DR. HAWES: But they didn't undergo re-cystoscopy.

20 DR. SNYDER: Patients did not routinely undergo
21 cystoscopy on follow-up evaluations.

22 DR. DONATUCCI: Were all the episodes or urinary
23 tract infection simple cystitis, or did any patient have an
24 upper tract infection?

25 MS. PETERSON: Tina, do you want to answer that?

1 MS. WITTCHOW: All the events of urinary tract
2 infection were simple cystitis. I can give you some
3 specifics as to the urinary tract infections and the ability
4 to resolve the infections. For our patient population, 88
5 percent of those UTIs were cured with one treatment of
6 antibiotics or one course of antibiotics, leaving about 8
7 percent that needed to use two courses of antibiotics to
8 cure, usually a switch in the type of antibiotic that was
9 being used, and 4 percent of the patient population had UTIs
10 resolved on their own, either because the patient chose not
11 to take antibiotics or chose to use other methods like
12 increase their fluid, changed their practices to see if they
13 could resolve it on their own.

14 So, they were fairly routine in the cure rate or
15 resolution of those UTIs.

16 DR. A. KALLOO: Ms. Newman.

17 MS. NEWMAN: I have two questions for you. You
18 said that your primary outcome variables have been change in
19 continence grade and pad weight, but you said your
20 reinjection criteria was quality of life.

21 Were those the same variables you looked at for
22 reinjecting women?

23 MS. WITTCHOW: Reinjection, to reiterate what Dr.
24 Snyder had said previously, reinjection was considered after
25 an entire follow-up. For instance, the criteria for a

1 follow-up would have been evaluating the continence status,
2 doing a pad weight, doing a quality of life only after six
3 and 12 month follow-up, doing a diary, and then evaluating
4 all of those in coming up with Stamey continence grade, as
5 well as discussing the need for re-treatment. So, all of
6 those factors were taken into consideration for re-
7 treatment.

8 MS. NEWMAN: The second question I have is you
9 have data on 18 months. What numbers do you have longer
10 term, what numbers as far as reinjection rate, how many
11 women you have long term, after 18 months, and what are you
12 doing with that?

13 MS. PETERSON: So, are you asking after 18 months,
14 how many?

15 MS. NEWMAN: What numbers you have on that, and
16 how long out are there?

17 MS. PETERSON: Right now we have about 30, a
18 little over 30 in each group, so about 65 patients that have
19 hit their 18 month in the report.

20 MS. NEWMAN: No, but I mean beyond 18 now.

21 MS. WITTCHOW: We have about 30 patients at the
22 24-month follow-up, as well as about 9 more at the 30-month
23 follow-up, and we have been, while the study has been open,
24 we continue to follow them every six months.

25 MS. NEWMAN: Do you have data beyond 18 months

1 then? Do you have data beyond those 18 months in a certain
2 cohort?

3 DR. SNYDER: That data is currently being
4 collected, but has not analyzed for purposes of this talk
5 today.

6 DR. N. KALLOO: Were you doing any ultrasound
7 evaluation for volume of post-void residuals?

8 DR. SNYDER: The standard BVI ultrasound or
9 catheterization were the standards by which sites used for
10 measuring post-void residual.

11 DR. N. KALLOO: Were you able to see the spheres
12 on ultrasound, did they have a typical pattern on
13 ultrasound?

14 DR. SNYDER: My personal experience was that,
15 number one, I didn't do the follow-ups because I was a
16 blinded physician, but there was no mention of that on the
17 ultrasound, but remember, this is not high-resolution
18 ultrasound.

19 DR. N. KALLOO: Like a bladder scanner?

20 DR. SNYDER: This was a bladder scanner, yes, and
21 my guess is, is that had one done intravaginal ultrasound
22 with a high resolution, 5 megahertz or so, that you would
23 have seen the particles.

24 DR. N. KALLOO: My concern would be certainly in a
25 male, for example, who still has his prostate in, how would

1 that patient be monitored? Were you able to feel any
2 difference on digital rectal exam in males?

3 DR. SNYDER: In my site, we had no non-post-
4 prostatectomy males, no TUR males who participated in the
5 study. In fact, we had no male patients in my study at all,
6 my site, so I can't answer that question.

7 DR. N. KALLOO: Is there anybody that can answer
8 that?

9 MS. WITTCHOW: The inclusion criteria for our
10 protocol required the male patients to be post-
11 prostatectomy, so we did not have any males in the study
12 that still had their prostate.

13 DR. SNYDER: So, TUR incontinence after a benign
14 prostate operation would not be a part of that cohort.

15 DR. N. KALLOO: I am thinking in terms of sort of
16 spinal cord injury patients or neurologic etiologies.

17 DR. SNYDER: Neurologically impaired patients were
18 excluded from the study.

19 DR. DONATUCCI: Pardon me if you have already
20 answered this, but there was a statistically significant
21 difference between the time to first re-treat and between
22 Durasphere and the control, at least as I read it in the
23 handout.

24 Was there any anatomic differences between the two
25 groups when you looked inside for the first re-treatment?

1 DR. SNYDER: Dr. Donatucci, can you just tell me
2 what -- rephrase your question again?

3 DR. DONATUCCI: I am referring specifically, let
4 me find it for you --

5 DR. HOLCOMB: Is that Table 33 on 45?

6 DR. DONATUCCI: No, actually, there is another
7 table a little later. Yes, I am sorry, it is 33 on 45, I
8 was looking at the wrong table, exactly. The time to first
9 and second injection was statistically different between the
10 two groups, and I am just asking whether there was anything
11 you found at the time. That just struck me, and I was
12 wondering what that was.

13 DR. SNYDER: I don't believe so. I believe what
14 this represents is a scheduling factor between the follow-up
15 visit and when the -- there was no defined time period when
16 the patients had to be injected following that evaluation,
17 so many times patients couldn't come in during certain
18 months of the year or at certain vacations, and so certain
19 patients were just put off for several weeks.

20 DR. DONATUCCI: Artifactual then.

21 DR. SNYDER: I think they are artifactual, yes.

22 DR. A. KALLOO: Was there a difference in the
23 quality of life scores between the two groups? I saw your
24 zero in one year, but compared to the two groups, was there
25 a difference?

1 DR. HOLCOMB: No, there wasn't, not any of the
2 follow-ups, and not at the 12-month follow-up between the
3 two groups.

4 DR. A. KALLOO: Is that surprising given the fact
5 that the urinary retention, et cetera, was higher?

6 DR. HOLCOMB: I don't know if it's surprising. It
7 probably reflects the fact that those didn't impact
8 significantly on the people's feelings.

9 DR. SNYDER: I think when you look at the quality
10 of life issues, it all is based upon or much of it is based
11 upon the expectations of the individual patient and how much
12 improvement that individual expects to make to be happy, and
13 for some patients, completely dry would be the only
14 acceptable result, and in other patients, a significant
15 reduction in incontinence and use of pads, et cetera, would
16 be a significant quality of life improvement.

17 DR. DIAMOND: I would like to go back to the
18 tissue reaction question. Can you tell me a little bit
19 about beta-glucan, how long it resides in the body, how it
20 is cleared? Is there anyone that has that information?

21 MS. PETERSON: Sure. I would like to have Dr.
22 Kirkemo answer that.

23 DR. A. KALLOO: If you could please introduce
24 yourself.

25 DR. KIRKEMO: My name is Aaron Kirkemo. I am a

1 urologist in private practice in St. Paul, Minnesota.

2 The beta-glucan, we do not have an enzyme in our
3 body, a glucanase enzyme to digest it, so if you look at the
4 histologic data from the animals, what happens is this
5 material is phagocytized, and you ultimately just see it
6 sitting in macrophages and histiocytes. It is just kind of
7 encapsulated as a foreign body.

8 The thing that is interesting, if you kind of look
9 at the tissue reaction over time, it looks very bland within
10 a very short period of time.

11 DR. DIAMOND: What is the time portion over which
12 it is phagocytized? Are we talking days or --

13 DR. KIRKEMO: If you look at the basic response at
14 least from the animal models, at seven days there is a bit
15 of an acute inflammatory response with both
16 polymorphonuclear leukocytes -- with both leukocytes and
17 lymphocytes.

18 If you look at the three-month data, by that time
19 point it is basically early deposition of collagen, mostly
20 histiocytes and a few macrophages, and by the time you get
21 out to six months it's basically just bland collagen. It
22 looks very benign.

23 DR. DIAMOND: So, at three months or six months is
24 there any beta-glucan that is not yet phagocytized?

25 DR. KIRKEMO: I can't say exactly. At least with

1 all the histology that I looked at, everything looked
2 incorporated.

3 DR. A. KALLOO: Could you state your financial
4 interest, please.

5 DR. KIRKEMO: I am a consultant for them.

6 DR. DIAMOND: Going back to the questions I was
7 asking earlier, then, about what is it that is providing the
8 durability, the comments, if it is gone pretty much at three
9 to six months, then, it is probably the particles where
10 collagen that develops, that is, what is acting is it is not
11 something that at least components of the device are not
12 persistent.

13 MS. PETERSON: And I think you are precisely
14 right, it's a combination of what you just said.

15 DR. SNYDER: And the pyrolytic beads obviously
16 composing --

17 DR. KIRKEMO: You see a volume of beads, and you
18 see mature collagen.

19 DR. DIAMOND: So, what then happens in those
20 patients who have continence or who get some improvement in
21 a month, but don't have improvement six months, a year, 18
22 months in the data that were presented to us?

23 DR. SNYDER: Clearly, that is a multifactorial
24 type of problem that may relate to changes in bladder
25 function, maybe not seen initially at one month, but

1 certainly at six months down the line, you can change the
2 compliance of the bladder, create some de novo urgency.

3 You can see disruption of the bleb and loss of the
4 implant, as you can with the control.

5 DR. DIAMOND: But the changes in the bladder, you
6 should have picked up on urodynamics. Did you see
7 differences like that?

8 DR. SNYDER: Urodynamics was performed at 12
9 months.

10 DR. DIAMOND: Right, and baseline beforehand.

11 DR. SNYDER: We did not see --

12 DR. DIAMOND: So, it is not changes in bladder
13 function then.

14 DR. SNYDER: No, it's not, but you are asking for
15 a theoretical of any given patient, what could potentially
16 be the cause, and what I am trying to say is that it may be
17 loss of implant bulk, it may be changes in the urethra, or
18 it may be other factors, such as pelvic relaxation that we
19 don't measure it is difficult to measure.

20 Clearly, there are multiple factors that could
21 cause that.

22 DR. DIAMOND: I was trying to be more than
23 theoretical in that part of the presentation described the
24 product as non-absorbable, and looking at the data over
25 time, 7.3.5, it looks like continence decreases actually.

1 Now, whether it is significant, I don't know, because I
2 don't think that analysis was done. Section 7.3.5. I am
3 sorry, that's not right. I am sorry, it's Table 19. I was
4 looking at the wrong place.

5 Analysis has been done there, comparing Durasphere
6 with control, but if you look at continence grade, you have
7 greater improvement in continence grade early on than you do
8 later on. At one month it is 1.1, and at 12 months and 18
9 months it is about 0.9, so you have about a 20 percent
10 reduction in continence grade from one month to 12 months.

11 DR. SNYDER: Yes, and it seems to be similar in
12 the control group, as well, and I once again would propose
13 that the mechanisms are not completely understood. We do
14 acknowledge that there is a decrease in continence grade,
15 and there is some loss in continence control that is gained
16 on initial injection that clearly happens over time. We do
17 lose some.

18 DR. A. KALLOO: What I would like to propose -- do
19 you have a question?

20 DR. N. KALLOO: I do. I actually have two
21 questions. Did you notice any granulomas in the area of the
22 injection?

23 DR. SNYDER: No.

24 DR. KIRKEMO: No. It was very interesting that
25 there really were not giant cell granulomas, granulomas like

1 you might see with lipid or something like that. It was
2 quite remarkable to me there was basically just bland
3 collagen within a period of about three months on.

4 DR. N. KALLOO: The other question that I had is I
5 noticed on your movie, on the video portion, you saw some of
6 the beads actually come out. You mentioned that the glucan
7 didn't come out, but I actually saw beads that came out, and
8 my concern would be these are biodegradable, is that
9 correct, the beads themselves, the spheres, the carbon-
10 coated spheres?

11 DR. KIRKEMO: Correct, they are not biodegradable.

12 DR. N. KALLOO: How would you go about monitoring
13 that, for example, over time, if those came out into the
14 urethra and sort of stuck around in that area, over time
15 that might set up a chronic reaction, and we know that the
16 tissue in that area was chronic reaction. Certainly, we are
17 concerned about things like squamous cell and that over
18 time.

19 So, my concern would be how would that be
20 monitored over time - or stone formation, for example?

21 DR. SNYDER: Sure. I think that is a very
22 thoughtful question. As I made a comment before, where I
23 was really surprised that we didn't run into problems was in
24 the bladder, that the dependent position of a bladder with a
25 mild Grade 1 cystocele, that one might see beads in the

1 bladder. At no point in any of the sites in any of the
2 patients was there free retention of carbon particles of
3 beads either in the urethra or in the bladder.

4 These beads are small enough that they get
5 excreted out with voiding, and the patients would report
6 that they had some sand, because to the naked eye it looks
7 like sand, when they voided, and they looked in the toilet.

8 DR. KIRKEMO: And then also from the standpoint of
9 kind of a chronic inflammatory sort of reaction, again, what
10 was seen is you would see macrophages kind of wrap around
11 the thing, an early granuloma formation, but then by six
12 months all the inflammatory cells were gone, and all you
13 would see would be a bead with just mature collagen around
14 it, and no signs of any chronic inflammatory process going
15 on whatsoever.

16 So, there was really no appearance of any chronic
17 foreign body reaction, you know, seen within a very short
18 period of time.

19 DR. SNYDER: And on follow-up, it is fair to say
20 that when one looked back into a urethra that had been
21 implanted for a secondary procedure, both the Durasphere
22 group and the control group showed amazingly well-healed
23 urethral mucosa except in the areas that had recently burst
24 blebs, and you saw some fraying of the mucosal tissue.

25 DR. KIRKEMO: And that is a phenomenon you see

1 with any bulking agent. If the mucosa becomes disrupted,
2 you will see sort of a roughened area.

3 DR. A. KALLOO: One final question.

4 DR. FOOTE: One quick question, and it kind of
5 goes back to the discussion before about why some patients
6 got better than others. Did you look back in your
7 demographic data of your initial groups to see if there were
8 some things in terms of demographics, in terms of what
9 patients did better than others?

10 DR. SNYDER: Sure. Would you address that?

11 MS. PETERSON: We did a logistic regression
12 analysis, and Rich will give you the result, and it is
13 actually in your book, as well.

14 DR. HOLCOMB: Dr. Foote, it's in Appendix A of the
15 panel pack that was presented, and we obviously were
16 interested in identifying which patients would tend to do
17 better than others, and as part of that, we did a
18 multivariable analysis and identified actually five baseline
19 factors that were associated with better success, and the
20 details of that analysis is presented there, but it's those
21 things that you would expect - people with worse
22 incontinence, that was a predictor for how well they did.

23 DR. A. KALLOO: One very last question.

24 DR. HAWES: For a rather ignorant
25 gastroenterologist, put things into a little bit of

1 perspective for me. The average age of these individuals
2 was 57 years old. You have provided us data that looks good
3 for 12 months.

4 What happens to these people long term? I mean do
5 you anticipate needing to reinject all these people after
6 two years? If you do reinject them, is there just fibrous
7 tissue, so you can't enter that subcutaneous space any
8 longer?

9 It seems to me that this whole area of injection
10 for incontinence begs for more long-term studies, and I am
11 wondering what your perspective is on that. I know your
12 data just addresses 12 months, but to me, as I assess this
13 as a treatment for patients, it seems to me that a longer
14 term perspective needs to be provided.

15 DR. HOLCOMB: Let me just address maybe two
16 subpoints. First of all, with regard to effective age of
17 patient, that did not turn out to be a predictor for success
18 in the study, so younger patients and older patients had
19 similar success profiles.

20 DR. HAWES: For 12 months.

21 DR. HOLCOMB: For 12 months. Actually, the data
22 in the tables, for example, Table 19, that was referred to
23 earlier, goes out to 18 months, and after that initial
24 decline after the first month, to date -- and, of course,
25 you are always limited by how far that you look out -- but

1 to date, it looks like we have a relatively stable
2 performance profile for patients out to 18 months and the 24
3 months, the initial data there suggests that, as well.

4 So, you can't say what will happen in five years,
5 but certainly the data we have to date suggests that you
6 have got a stable persistent response with the Durasphere
7 patients.

8 DR. SNYDER: I think based upon previous intra-
9 urethral implant bulking agents, such as teflon and
10 Contigen, we don't typically see fibrosis. It would be a
11 very unusual thing to see in the urethra looking out beyond
12 a year.

13 The potential of this device, the advantages
14 besides the decrease and immunogenic nature of it, is the
15 fact that the carbon beads may stay long enough to give a
16 longer lasting result, and that is yet to be determined, but
17 as Rich just stated, at 18 months it look like there is some
18 durability at this point, but this is stopping the clock at
19 one moment, and we will have to see.

20 DR. A. KALLOO: We will now take a short, 10-
21 minute break and reconvene promptly at 11:20.

22 [Recess.]

23 DR. A. KALLOO: If I could have everyone please
24 take their seats.

25 The meeting will now reconvene with an open

1 committee discussion. Dr. Jenelle E. Foote will give a
2 clinical overview of incontinence.

3 Dr. Foote.

4 **Clinical Overview of Incontinence**

5 **Jenelle E. Foote, M.D.**

6 DR. FOOTE: I am very happy to be here. I
7 appreciate this opportunity to address the panel and address
8 guests, and I felt that today it would be important to put
9 the current discussions in the framework of the work that
10 has been done on incontinence of all sorts, not just stress
11 incontinence, and so what I have prepared for this morning
12 is a review of the evaluation and treatment of urinary
13 incontinence in the female.

14 [Slide.]

15 As was mentioned earlier, urinary incontinence is
16 a big problem affecting about 13 million Americans, most of
17 which are women. A quarter of these women are in this age
18 group, and incontinence affects 50 percent of the elderly.

19 [Slide.]

20 There are implications in regard to incontinence
21 to include emotional problems, social activity, skin
22 problems, as well as cost, and this cost is not only in
23 terms of medical treatment, that that individual may get
24 from a physician or from a hospital or another health care
25 provider, but also in the use of pads and padding and

1 bedding that need to be changed to deal with this problem.

2 [Slide.]

3 Incontinence occurs because there is problems in
4 regards to the storage of urine and urinary tract,
5 specifically, the lower urinary tract, the bladder and
6 urethra.

7 [Slide.]

8 If you can remember this little summary here, this
9 will help you understand many of the times when urologists
10 discuss continence, remember that is a function of normal
11 bladder function plus normal sphincteric function. You need
12 to have both of them working well to allow for continence.

13 [Slide.]

14 Keep in mind also that the neurologic control over
15 the lower urinary tract is essential to allow for
16 continence, hence, the problems with continence in
17 individuals who have neurogenic problems.

18 [Slide.]

19 In terms of the etiologies, including neurogenic
20 etiologies, trauma either from surgery or obstetrical
21 trauma, as well as certain congenital conditions and
22 hormonal conditions, can be associated with incontinence.

23 [Slide.]

24 In regards to the diagnosis, the workup for the
25 typical urologist or other health care provider evaluating

1 incontinence, a good history, as well as a physical
2 examination is necessary, a urinalysis with a culture and
3 sensitivity being done if there is worry of infection, with
4 urodynamics being the functional test that is done in many
5 cases to help determine the type of incontinence and so
6 guide therapy.

7 [Slide.]

8 There are four basic types of incontinence, and I
9 show this slide to illustrate that there is overlap, and so
10 the evaluation of a patient with incontinence can be quite
11 complex as you can have a patient with more than one type.
12 I am going to be talking specifically this morning about
13 urge incontinence, then briefly about overflow incontinence,
14 and lastly, stress incontinence.

15 I am not going to specifically talk about
16 functional incontinence, but suffice as to say that
17 functional incontinence is associated with individuals who
18 have problems with the habit of toileting. This includes
19 individuals who have physical disabilities, as well as
20 cognitive disabilities that make toileting difficult.

21 [Slide.]

22 In regard to urgency incontinence, this woman's
23 face says it all. Essentially, an overactive bladder is
24 acting without the owner's permission, if you will, and
25 contracting, allowing for the expulsion of urine. If the

1 external sphincter is not competent enough to prevent the
2 flow of urine, if the external sphincter is tight enough to
3 prevent the leakage of urine, the individual can experience
4 suprapubic discomfort, as well as pain and a feeling or
5 urgency.

6 [Slide.]

7 These patients can be characterized as having the
8 so-called overactive bladder. When you see this term, this
9 refers to a situation where the individual experiences these
10 symptoms without any known neurologic or metabolic cause.

11 [Slide.]

12 In terms of the treatment for the overactive
13 bladder or to instability or to hyperreflexia, there is a
14 lot of different terms that you will see used for this.
15 Another term is hypertonic bladder. They include the use of
16 pads, of course, behavioral modification, pharmacologic
17 therapy is the mainstay of therapy in 1999. Also, used is
18 electrostimulation, as well as a variety of other surgical
19 treatments.

20 [Slide.]

21 As I mentioned before, drugs are the mainstay of
22 therapy. These drugs tend to be anticholinergic and a
23 spasmodic in character.

24 [Slide.]

25 The three main generically available drugs are

1 seen here. In the last two or three years, we have seen a
2 number of other drugs that have been recently developed to
3 cut down on the side effects associated with these drugs,
4 which are predominantly anticholinergic. These patients
5 many times have a dry mouth and constipation.

6 One of the newer treatments for urgency and
7 urgency incontinence is use of sacral nerve stimulation, and
8 as Mr. St. Pierre talked earlier, this procedure was
9 recently approved.

10 [Slide.]

11 This form of therapy allows for stimulation of the
12 pelvic nerves that go to the pelvic floor.

13 [Slide.]

14 Via the S3 nerve, and in doing so, affects
15 incontinence.

16 [Slide.]

17 The next type of incontinence I would like to
18 review is called overflow incontinence. In contrast to the
19 previous type of incontinence, this incontinence is
20 characterized by a bladder that can't empty either because
21 there is some element of obstruction at the level of the
22 bladder neck or that the bladder has lost its tone and does
23 not push adequately to empty.

24 Essentially, what empties out in this individual
25 is the amount of urine that exceeds the capacity of the

1 bladder, hence, the word overflow.

2 [Slide.]

3 In this condition, this is seen not uncommonly in
4 long-standing diabetes, as well as certain neurogenic
5 dysfunction, and in able-bodied individuals, bladder habits
6 that delay voiding, the so-called nurses' bladder.

7 [Slide.]

8 Treatments for this include bladder training, not
9 exactly as you see here, but basically, the individual is
10 taught or prompted to void on a regular basis.

11 [Slide.]

12 Timed voiding for patients who are not cognitively
13 impaired by teaching the patient to go by their watches, of
14 how they feel, can be very useful for this disorder.

15 [Slide.]

16 And for individuals who cannot empty despite those
17 types of programs, catheterization is the preferred method
18 of treatment.

19 [Slide.]

20 Stress incontinence is the type of leakage that we
21 think about when we think about stressful maneuvers like in
22 this little cartoon, the woman lifting the groceries out of
23 the back of a car, coughing, sneezing, laughing, jumping,
24 there is pressure from the abdominal muscles that is exerted
25 on the bladder. If the bladder is full, and the bladder

1 neck or supportive structures are incompetent, there can be
2 leakage of urine.

3 [Slide.]

4 In this condition, generally, the individual
5 reports small losses of urine when doing these so-called
6 stressful maneuvers, and typically, the individual is dry at
7 night or when they are not engaged in stressful maneuvers.

8 [Slide.]

9 In regards to the evaluation of stress
10 incontinence, one is concerned about how much pressure it
11 takes to open up the bladder neck, and this has been
12 described a number of ways. Closure pressure has been used
13 to quantify this, as well as leak point pressure.

14 [Slide.]

15 In terms of the treatments, the include pelvic
16 floor exercise training, use of prostheses, and what I call
17 the patches and the plugs, as well as various surgical
18 options, and we are going to go over those briefly.

19 [Slide.]

20 The use of pelvic floor exercises is recommended,
21 and I certainly recommend it for the primary treatment in
22 most women presenting to me who have stress incontinence,
23 because you may not need to do this if the person can
24 strengthen the pelvic floor and decrease incidents of
25 incontinence.

1 [Slide.]

2 These so-called Kegel exercises have been
3 rejuvenated and --

4 [Slide.]

5 -- are being done with a variety of aids to make
6 them more effective. This, for example, is the use of a
7 type of weighted cone that I call barbells for the pelvic
8 floor, that can be used to help make these pelvic floor
9 exercises more effective.

10 [Slide.]

11 In addition, the use of biofeedback and
12 electrostimulation can also make these exercises more
13 effective.

14 [Slide.]

15 There have been a number of studies looking at the
16 benefit of electrostimulation for the treatment of
17 incontinence. If you look here under stress incontinence,
18 although the success rate in regards to cure is moderate,
19 there is a variety of improvement rates that run the gamut
20 from 20 to 100 percent.

21 [Slide.]

22 As regards to certain patches and plugs, I have a
23 couple of them here that I am showing to you, that are not
24 commercially available right now. The panel may be hearing
25 about some in the future. I do know that there are some in

1 commercial development.

2 [Slide.]

3 The purpose of these devices is to stem the flow
4 of urine by using a device either inserted in the vagina or
5 in the urethra to effect continence.

6 [Slide.]

7 Next, I would like to talk briefly about something
8 that you may have heard about, and that is the types of
9 stress urinary incontinence. Classically, urinary
10 incontinence has been graded from a Type zero to a Type III.
11 You are hearing less and less of that in the literature
12 these days.

13 [Slide.]

14 Suffice as to say the type of incontinence that
15 you have heard about the most often is the so-called Type
16 III incontinence, also known in today's parlance as
17 intrinsic sphincteric deficiency, and you heard that term
18 discussed at the discussion earlier today.

19 In terms of causes of Type III stress incontinence
20 or ISD, it includes previous pelvic surgery, radiation
21 therapy, neurogenic dysfunction, as well as other kinds of
22 causes to include the lack of estrogen in women who are
23 postmenopausal.

24 [Slide.]

25 In regards to the current thinking, again, at one

1 time we were very rigid and tried to put patients in one
2 camp or the other, i.e., patients who have Type zero to II
3 stress incontinence in which anatomic malposition or
4 weakness of the pelvic floor supporting the bladder was felt
5 to be the problem, and the other camp being that of ISD Type
6 III incontinence or that of the dysfunctional urinary
7 sphincter being the cause.

8 What we understand now is that it is more of a
9 combination of the two in most patients, and so that we are,
10 in terms of urologists, are changing our ways in terms of
11 how we are approaching patients, appreciating that patients
12 will likely have a combination of these two types of factors
13 contributing to stress incontinence. I am talking
14 specifically about women in this regard.

15 Next, in regards to the typical and classic
16 bladder neck suspensions that have been suggested and are
17 still done for the treatment of Type zero through Type II
18 stress incontinence, they are called a variety of different
19 names. Those of you in the audience may recognize the name
20 of some of these operations that are named after surgeons.
21 Surgeons are egotistical, so they like to put their names on
22 procedures.

23 [Slide.]

24 Just to show you what these operations try to do
25 by restoring the anatomy of the pelvic floor. In this

1 little cartoon, you can see a bladder here with a bladder
2 neck and urethra here in this side view of a woman's pelvis.
3 Note here the pubic bone and note that there is a distance
4 in between the bladder neck and the pubic bone.

5 This distance is theoretically felt to be due to
6 something called pelvic relaxation or weakness of the pelvic
7 floor, such that the bladder neck is a fair distance away
8 from the pubic bone.

9 [Slide.]

10 What the surgical action attempt to do is to
11 restore this anatomy, i.e., to bring the bladder neck close
12 to the pubic bone.

13 [Slide.]

14 What I would like today is just to briefly talk
15 about a study that was commissioned by the AUA to look at
16 the long-term results. There was a question, and an
17 excellent question, earlier today about what is the long-
18 term benefit of these different types of technologies that
19 are being proposed for stress incontinence, and, as
20 urologists, we have recognized the importance of looking at
21 long-term data.

22 [Slide.]

23 In this particular study, I am just going to
24 highlight two slides from this study. There were two types
25 of operations that were felt to have the best long-term

1 success rate. In this study, they looked at a number of
2 studies in the literature that were felt to be good studies,
3 that had some objective measures for inclusion, their
4 criteria, as well as success, and they found that the
5 retropubic suspensions, known as the MMK's, the Birch
6 procedures, as well as the Richardson repairs, were felt to
7 have fairly good long-term success rates, about 90 percent
8 going at greater than 48 months.

9 [Slide.]

10 For those non-surgeons in the audience, what these
11 operations do is to bring the bladder neck close to the
12 pubic bone, as I mentioned earlier. This is a picture
13 showing a Birch procedure with the foot of the patient being
14 here, the head of the patient being here. Here is the
15 bladder, here is some fascia on either side of the bladder
16 that is being sutured up to this ligament on either side of
17 the pelvis, so-called Cooper's ligament.

18 You can see that the bladder is being suspended by
19 this fascia and therefore, the bladder neck is being brought
20 close to the pubic bone.

21 [Slide.]

22 On the side view you can see a little bit more
23 dramatically in this cartoon how that is represented.

24 [Slide.]

25 In the next category of this study that showed the

1 procedure having the best long-term success rates was that
2 of the so-called sling procedure, and at 48 months you can
3 see this procedure had a median of probability of cure, dry
4 or improved, of 87 percent.

5 [Slide.]

6 In this particular operation, a piece of fascia or
7 other material is placed underneath the bladder neck with
8 the purpose of lifting the bladder neck in addition to
9 restoring the anatomic proximity of the bladder neck to the
10 pubic bone, also giving some coaptation of the bladder neck
11 area and proximal urethra.

12 [Slide.]

13 The artificial urinary sphincter is a device that
14 has been popularized for the treatment of stress
15 incontinence or ISD. It is used mostly in men. In women,
16 there is a relatively high rate of erosion with these
17 devices. As you may know, this is a hydraulic device that
18 involves the use of fluid that is cycled through a pump
19 device to a cuff that is placed around the urethra that
20 affects continence.

21 [Slide.]

22 In regards to the injections that we are
23 discussing today, the way that those are felt to work is
24 through a bulking action, and you saw some fairly dramatic
25 pictures earlier in the presentation, but in this cartoon I